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By Authority of the
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APPROV

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR §1.53(c).

Express Mail No. EL904267984US	Docket No. 02-280	Type a plus sign (+) inside this box:	+

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TITLE OF THE INVENTION (280 character maximum)

Human Adam-10 Inhibitors

CUSTOMER NUMBER

20306
PATENT TRADEMARK OFFICE

McDonnell Boehnen Hulbert & Berghoff

ENCLOSED APPLICATION PARTS (check all that apply)

☒ Specification Number of Pages 63 ☐ Drawings Number of Sheets

☒ Other: Patent Data Sheets (3 sheets), return receipt postcard

METHOD OF PAYMENT FOR THIS PROVISIONAL APPLICATION FOR PATENT

☐ Applicant claims small entity status. See 37 CFR 1.27 ☐ A check or money order is enclosed to cover the Provisional Filing Fee. ☒ The Commissioner is hereby authorized to charge filing fees and credit Deposit Account Number: **13-2490.**	PROVISIONAL APPLICATION FOR PATENT FILING FEE AMOUNT ($)	160.00

CERTIFICATE OF MAILING

I hereby certify that, under 37 CFR § 1.10, I directed that the correspondence identified above be deposited with the United States Postal Service as "Express Mail Post Office to Addressee," addressed to the. Commissioner for Patents, Box Provisional Patent Application, Washington, DC 20231, on the date indicated below.

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government
_X_ No. _____ Yes, the name of the U.S. Government agency and the Government contract number are: _____

Respectfully submitted,

SIGNATURE: _____ Date: June 12, 2002

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☒ Additional inventors are being named on separately numbered sheets attached hereto.

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Application Information

Title Line One::	Human Adam-10 Inhibitors
Title Line Two::	
Total Drawing Sheets::	0
Formal Drawings?::	
Application Type::	Provisional
Docket Number::	02-280

Representative Information

Representative Customer Number 020306

HUMAN ADAM-10 INHIBITORS

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] The present invention is in the field of agents that inhibit human ADAM-10 (also known as human Kuzbanian) and their use in the treatment of cancer, arthritis, and diseases related to angiogenesis.

Summary of the Related Art

[0002] Cell-cell interactions play an important role in regulating cell fate decisions and pattern formation during the development of multicellular organisms. One of the evolutionarily conserved pathways that plays a central role in local cell interactions is mediated by the transmembrane receptors encoded by the Notch (N) gene of Drosophila, the lin-12 and glp-1 genes of C. elegans, and their vertebrate homologs (reviewed in Artavanis-Tsakonas, S., et al. (1995) Notch Signaling. Science 268, 225-232), collectively hereinafter referred to as NOTCH receptors. Several lines of evidence suggest that the proteolytic processing of NOTCH receptors is important for their function. For example, in addition to the full length proteins, antibodies against the intracellular domains of NOTCH receptors have detected C-terminal fragments of 100-120 kd; *see, e.g.*, Fehon, R. G., et al. (1990). Cell 61, 523-534; Crittenden, S. L., et al. (1994). Development 120, 2901-2911; Aster, J., et al. (1994) Cold Spring Harbor Symp. Quant. Biol. 59, 125-136; Zagouras, P., et al.(1995). Proc. Natl. Acad. Sci. U.S.A. 92, 6414-6418; and Kopan, R., et al. (1996). Proc. Natl. Acad. Sci. U.S.A. 93, 1683-1688. However, the mechanism(s) of NOTCH activation have been hitherto largely unknown.

[0003] During neurogenesis, a single neural precursor is singled out from a group of equivalent cells through a lateral inhibition process in which the emerging neural precursor cell prevents its neighbors from taking on the same fate (reviewed in Simpson, P. (1990). Development 109, 509-519). Genetic studies in Drosophila have implicated a group of "neurogenic genes" including N in lateral inhibition. Loss-of-function mutations in any of the neurogenic genes result in hypertrophy of neural cells at the expense of epidermis (reviewed in Campos-Ortega, J. A. (1993) In: The Development of *Drosophila melanogaster* M. Bate and A. Martinez-Arias, eds. pp. 1091-1129. Cold Spring Harbor Press.).

[0004] Rooke, J., Pan, D. J., Xu, T. and Rubin, G. M. (1996). Science 273, 1227-1231, discloses neurogenic gene family, kuzbanian (kuz). Members of the KUZ family of proteins are shown to

belonging to the recently defined ADAM family of transmembrane proteins, members of which contain both a disintegrin and metalloprotease domain (reviewed in Wolfsberg, T. G., et al. (1995). J. Cell Biol. 131, 275-278, see also Blobel, C. P., et al. (1992). Nature 356, 248-252, 1992; Yagami-Hiromasa, T., et al. (1995). Nature 377, 652-656; Black, R. A., et al. (1997). Nature 385, 729-733, 1997; and Moss, M. L., et al. (1997). Nature 385, 733-736; *see also* U.S. 5,922,546 and U.S. 5,935,792).

[0005] Genes of the ADAM family encode transmembrane proteins containing both metalloprotease and disintegrin domains (reviewed in Black and White, 1998 Curr. Opin. Cell Biol. *10*, 654-659; Wolfsberg and White, 1996 Dev. Biol. *180*, 389-401), and are involved in diverse biological processes in mammals such as fertilization (Cho et al., 1998 Science *281*, 1857-1859), myoblast fusion (Yagami-Hiromasa et al., 1995 Nature *377*, 652-656) and ectodomain shedding (Moss et al., 1997 Nature *385*, 733-736; Black et al., 1997 Nature *385*, 729-733; Peschon et al., 1998 Science *282*, 1281-1284). The Drosophila *kuzbanian* (*kuz*) gene represents the first ADAM family member identified in invertebrates (Rooke et al., 1996 Science *273*, 1227-1231). Previous genetic studies showed that *kuz* is required for lateral inhibition and axonal outgrowth during Drosophila neural development (Rooke et al., 1996; Fambrough et al., 1996 PNAS.USA *93*, 13233-13238.; Pan and Rubin, 1997 Cell *90*, 271-280; Sotillos et al., 1997 Development *124*, 4769-4779). Specifically, during the lateral inhibition process, *kuz* acts upstream of *Notch* (Pan and Rubin, 1997; Sotillos et al., 1997), which encodes the transmembrane receptor for the lateral inhibition signal encoded by the *Delta* gene. More recently, a homolog of *kuz* was identified in C. elegans (*SUP-17*) that modulates the activity of a C. elegans homolog of Notch in a similar manner (Wen et al., 1997 Development *124*, 4759-4767).

[0006] Vertebrate homologs of *kuz* have been isolated in Xenopus, bovine, mouse, rat and human. The bovine homolog of KUZ (also called MADM or ADAM 10) was initially isolated serendipitously based on its *in vitro* proteolytic activity on myelin basic protein, a cytoplasmic protein that is unlikely the physiological substrate for the bovine KUZ protease (Howard et al., 1996 Biochem. J. *317*, 45-50). Expression of a dominant negative form of the murine *kuz* homolog (*mkuz*) in Xenopus leads to the generation of extra neurons, suggesting an evolutionarily conserved role for *mkuz* in regulating Notch signaling in vertebrate neurogenesis (Pan and Rubin, 1997). U.S. patent application. No. 09/697,854, to Pan *et al.*, filed October 27, 2000, discloses that *mkuz* mutant mice die around embryonic day (E) 9.5, with severe defects in the nervous system, the paraxial mesoderm

the yolk sac vasculature. In the nervous system, *mkuz* mutant embryos show ectopic neuronal differentiation. In the paraxial mesoderm, *mkuz* mutant embryos show delayed and uncoordinated segmentation of the somites. These phenotypes are similar to those of mice lacking *Notch-1* or components of the Notch pathway such as *RBP-Jk* (Conlon et al, 1995, Development *121*, 1533-1545; Oka et al., 1995), indicating a conserved role for *mkuz* in modulating Notch signaling in mouse development. Furthermore, no visible defect was detected in Notch processing in the *kuz* knockout animals. In addition to the neurogenesis and somitogenesis defect, *mkuz* mutant mice also show severe defects in the yolk sac vasculature, with an enlarged and disordered capillary plexus and the absence of large vitelline vessels. Since such phenotype has not been observed in mice lacking *Notch-1* or *RBP-Jk* (Swiatek et al., 1994 Genes Dev *15*, 707-719; Conlon et al, 1995; Oka et al., 1995 Development *121*, 3291-3301), Pan *et al.* determined that this phenotype reveals a novel function of *mkuz* that is distinct from its role in modulating Notch signaling, specifically, that *kuz* plays an essential role for an ADAM family disintegrin metalloprotease in mammalian angiogenesis.

[0007] In view of the important role of KUZ (ADAM-10) in biological processes and disease states, inhibitors of this protein are desirable.

[0008] All patents, applications, and publications recited herein are hereby incorporated by reference in their entirety.

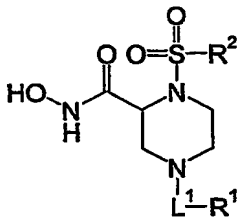
SUMMARY OF THE INVENTION

[0009] The present invention provides compounds useful for inhibiting the ADAM-10 protein. Such compounds are useful in the *in vitro* study of the role of ADAM-10 (and its inhibition) in biological processes. The present invention also comprises pharmaceutical compositions comprising one or more ADAM-10 inhibitors according to the invention in combination with a pharmaceutically acceptable carrier. Such compositions are useful for the treatment of cancer, arthritis, and diseases related to angiogenesis. Correspondingly, the invention also comprises methods of treating forms of cancer, arthritis, and diseases related to angiogenesis in which ADAM-10 plays a critical role.

[0010] The foregoing merely summarizes certain aspects of the invention and is not intended to be limiting.

DETAILED DESCRIPTION OF THE INVENTION

[0011] The present invention comprises inhibitors of ADAM-10. In one embodiment, the invention comprises a compound of structural formula I:



I

and pharmaceutically acceptable salts, esters, amides, and prodrugs thereof wherein

L^1 is -C(O)-, -$S(O)_2$-, or -$(CH_2)_n$- wherein n is 0, 1, 2, or 3;

R^1 is -OR^{11}, -$(CH_2)_nR^{11}$, -$C(O)R^{11}$, or -$NR^{12}R^{13}$;

R^{11}, R^{12}, and R^{13} independently are

a) R^{50};

b) saturated or mono- or poly- unsaturated C_5-C_{14}-mono- or fused poly- cyclic hydrocarbyl, optionally containing one or two annular heteroatoms per ring and optionally substituted with one or two R^{50} substituents;

c) C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, or -C(O)H, each of which is optionally substituted with one, two or three substituents independently selected from R^{50} and saturated or mono- or poly- unsaturated C_5-C_{14}-mono- or fused poly- cyclic hydrocarbyl, optionally containing one or two annular heteroatoms per ring and optionally substituted with one, two or three R^{50} substituents;

or R^{12} and R^{13} together with the N to which they are covalently bound, a C_5-C_6 heterocycle optionally containing a second annular heteroatom and optionally substituted with one or two R^{50} substituents;

R^2 is R^{21}-L^2-R^{22};

R^{21} is saturated or mono- or poly- unsaturated C_5-C_{14}-mono- or fused poly- cyclic hydrocarbyl, optionally containing one or two annular heteroatoms per ring and optionally substituted with one, two, or three R^{50} substituents;

L^2 is -O-, -C(O)-, -CH_2-, -NH-, -$S(O_2)$- or a direct bond;

R^{22} is saturated or mono- or poly- unsaturated C_5-C_{14}-mono- or fused poly- cyclic hydrocarbyl, optionally containing one or two annular heteroatoms per ring and optionally substituted with one, two, or three R^{50} substituents; and

R^{50} is R^{51}-L^3-$(CH_2)_n$-;

L^3 is -O-, -NH-, -S-, -C(O)-, -C(O)O-, -C(O)NH-, -OC(O)-, -NHC(O)-, or a direct bond;

R^{51} is -H, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, halo, -OH, $-NH_2$, -SH, $-CO_2H$, -CN, $-NO_2$, or $-SO_3H$;

provided that an O or S is not singly bonded to another O or S.

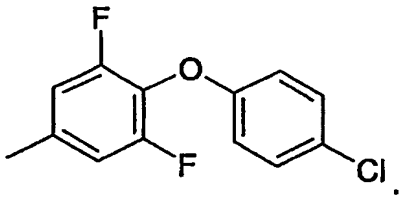
[0012] In a preferred embodiment according to paragraph [0011] wherein L^1 is -C(O)-.

[0013] In a preferred embodiment according to paragraph [0012] R^1 is $-OR^{11}$. More preferably R^1 is C_1-C_6-alkoxy-C_1-C_6-alkoxy; and still more preferably R^1 is methoxyethoxy.

[0014] In another preferred embodiment according to claim [0011], L^1 is $-S(O)_2$-.

[0015] In a preferred embodiment according to paragraph [0014] R^2 is phenoxyphenyl wherein each phenyl is optionally substituted with one or two R^{50} substituents. More preferably the R^{50} substituents are halo.

[0016] In one preferred embodiment, the compound is:

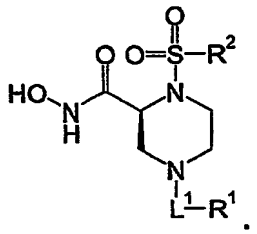


[0017] In another preferred embodiment according to paragraph [0011] wherein the saturated or mono- or poly- unsaturated C_5-C_{14}-mono- or fused poly- cyclic hydrocarbyl containing one or two annular heteroatoms per ring are selected from the group consisting of morpholinyl, piperazinyl, homopiperazinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, furyl, thienyl, pyranyl, isobenzofuranyl, chromenyl, pyrrolyl, imidazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl, oxadiazolyl, indolyl, quinolinyl, carbazolyl, acrydinyl, and furazanyl, optionally substituted with one or two R^{50} substituents.

[0018] In another preferred embodiment according to paragraph [0011], R^{12} and R^{13}, together with the N to which they are covalently bound, form a heterocycle selected from the group consisting of morpholinyl, piperazinyl, homopiperazinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, pyrrolyl, imida-

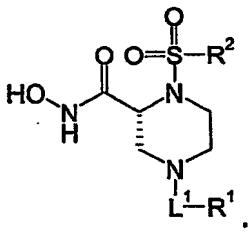
, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl, oxadiazolyl, indolyl, quinolinyl, carbazolyl, acrydinyl, and furazanyl, optionally substituted with one or two R^{50} substituents.

[0019] In another preferred embodiment, the invention comprises the compound according to paragraph [0011] having the stereochemistry of structure **II**:



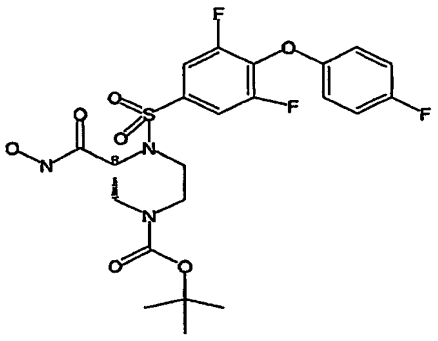
II

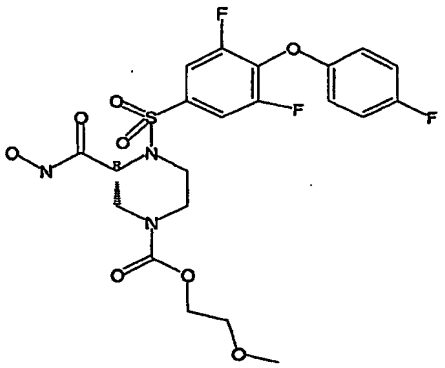
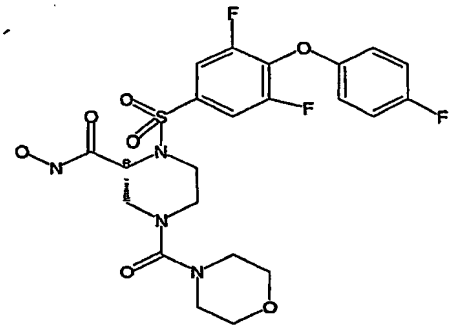
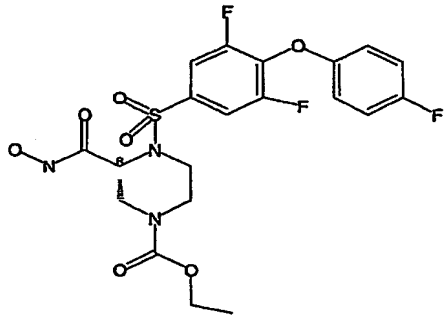
[0020] In another preferred embodiment of the compound according to paragraph [0011] is the compound having the stereochemistry of structure **III**:

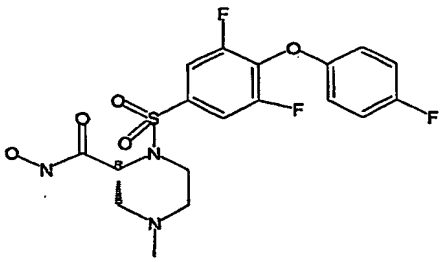
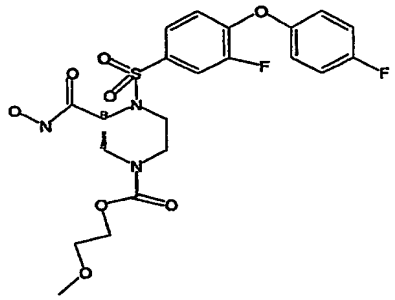
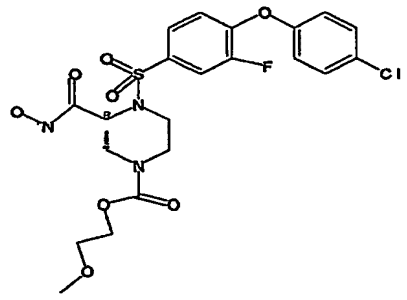


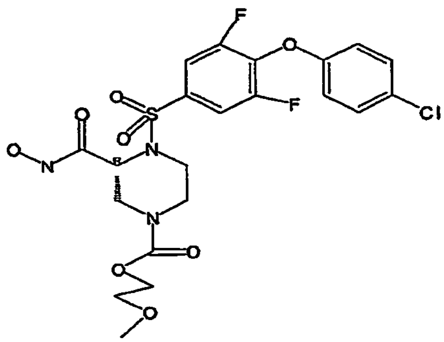
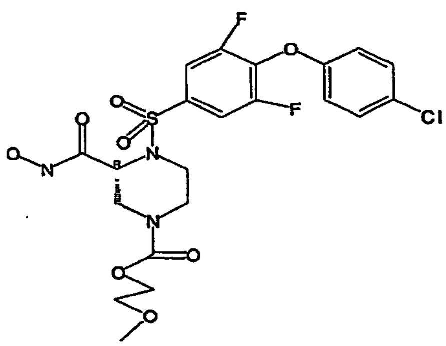
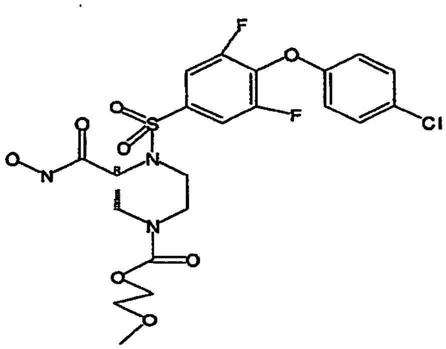
III

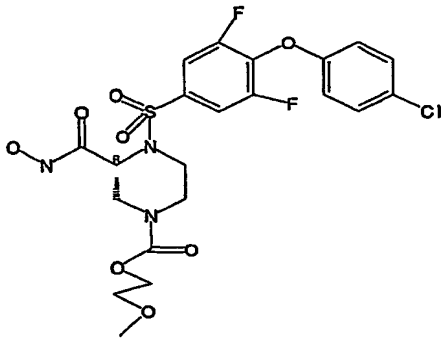
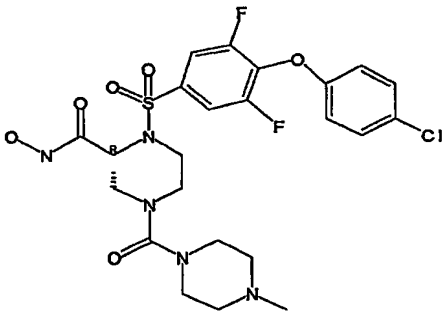
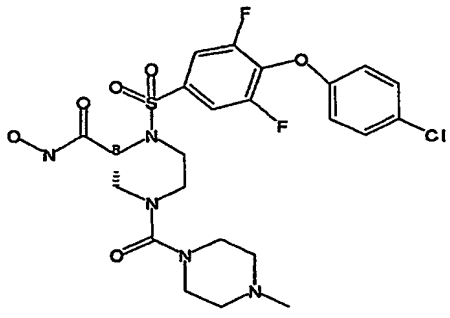
[0021] Particularly preferred compounds of the invention are those described in paragraph [0011] selected from the following table:

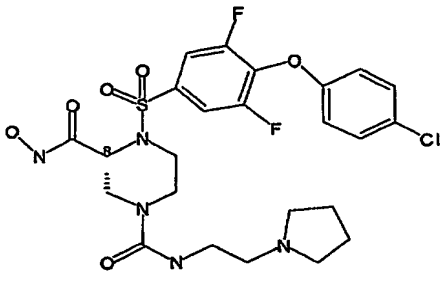
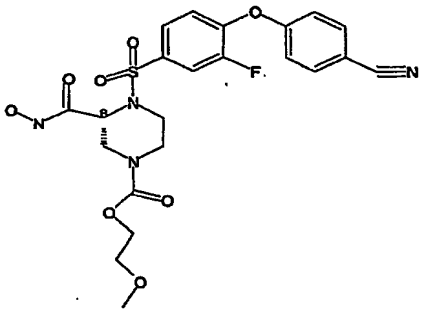
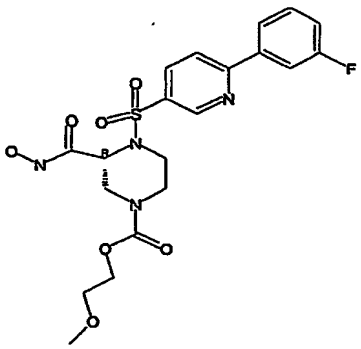
	tert-butyl (3R)-4-{[3,5-difluoro-4-(4-fluorophenoxy)phenyl]sulfonyl}-3-[(hydroxyamino)carbonyl]-1-piperazinecarboxylate,

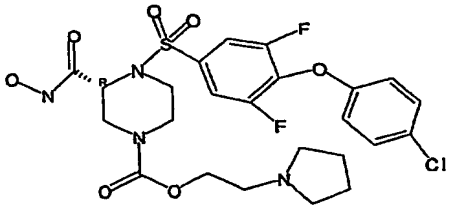
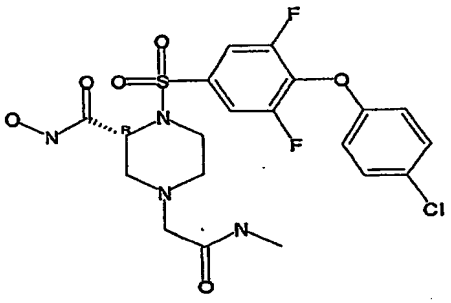
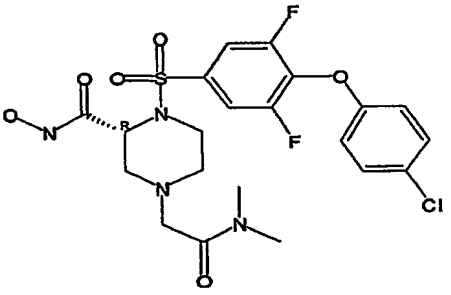
	2-methoxyethyl (3R)-4-{[3,5-difluoro-4-(4-fluorophenoxy)phenyl]sulfonyl}-3-[(hydroxyamino)carbonyl]-1-piperazinecarboxylate,
	(2R)-1-{[3,5-difluoro-4-(4-fluorophenoxy)phenyl]sulfonyl}-N-hydroxy-4-(4-morpholinylcarbonyl)-2-piperazinecarboxamide,
	ethyl (3R)-4-{[3,5-difluoro-4-(4-fluorophenoxy)phenyl]sulfonyl}-3-[(hydroxyamino)carbonyl]-1-piperazinecarboxylate,

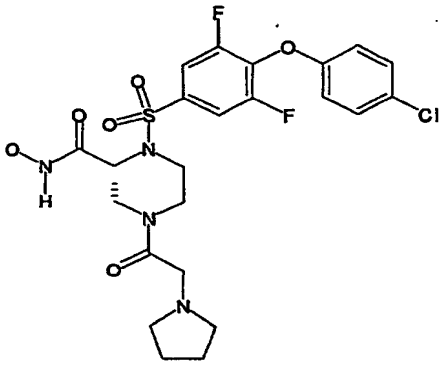
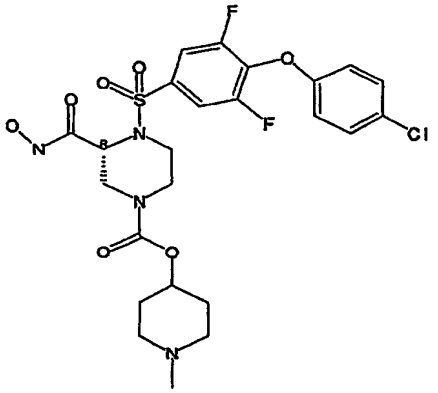
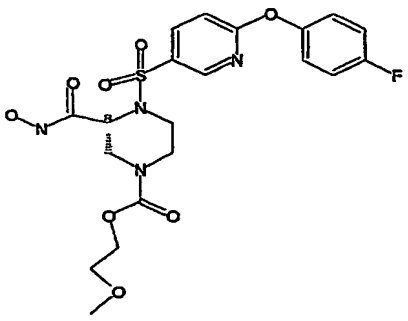
	(2R)-1-{[3,5-difluoro-4-(4-fluorophenoxy)phenyl]sulfonyl}-N-hydroxy-4-methyl-2-piperazinecarboxamide,
	2-methoxyethyl (3R)-4-{[3-fluoro-4-(4-fluorophenoxy)phenyl]sulfonyl}-3-[(hydroxyamino)carbonyl]-1-piperazinecarboxylate,
	2-methoxyethyl (3R)-4-{[4-(4-chlorophenoxy)-3-fluorophenyl]sulfonyl}-3-[(hydroxyamino)carbonyl]-1-piperazinecarboxylate,

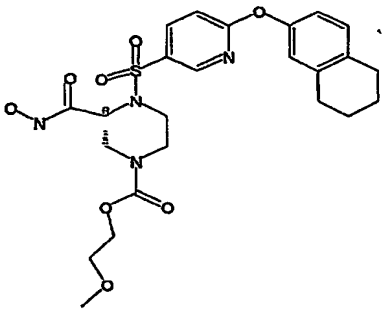
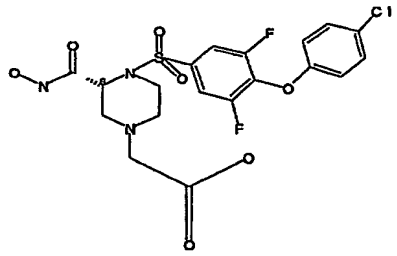
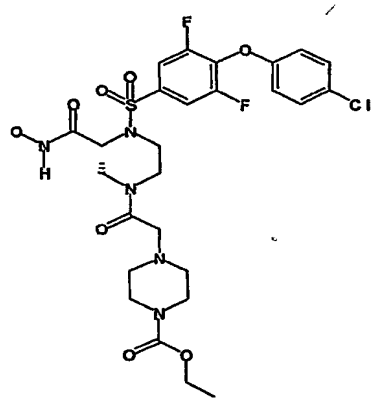
	2-methoxyethyl (3R)-4-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-3-[(hydroxyamino)carbonyl]-1-piperazinecarboxylate,
	2-methoxyethyl (3R)-4-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-3-[(hydroxyamino)carbonyl]-1-piperazinecarboxylate,
	2-methoxyethyl (3R)-4-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-3-[(hydroxyamino)carbonyl]-1-piperazinecarboxylate,

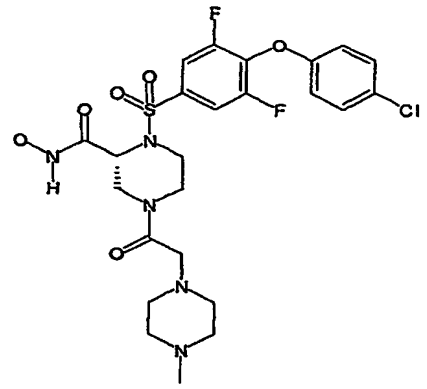
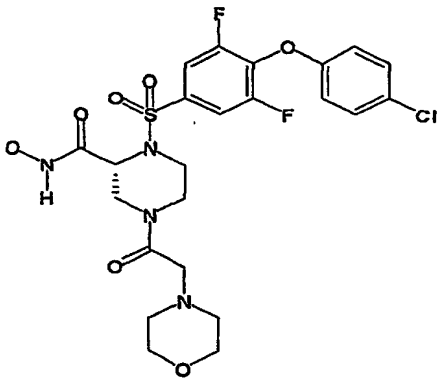
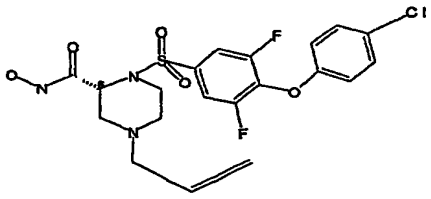
	2-methoxyethyl (3R)-4-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-3-[(hydroxyamino)carbonyl]-1-piperazinecarboxylate,
	(2R)-1-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-N-hydroxy-4-[(4-methyl-1-piperazinyl)carbonyl]-2-piperazinecarboxamide,
	(2R)-1-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-N-hydroxy-4-[(4-methyl-1-piperazinyl)carbonyl]-2-piperazinecarboxamide,

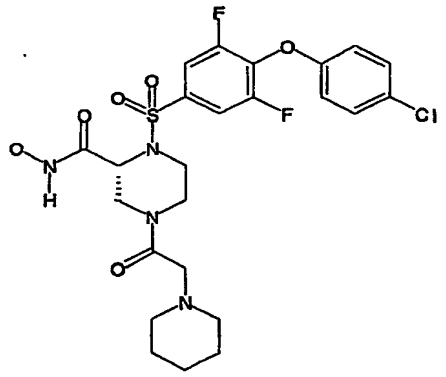
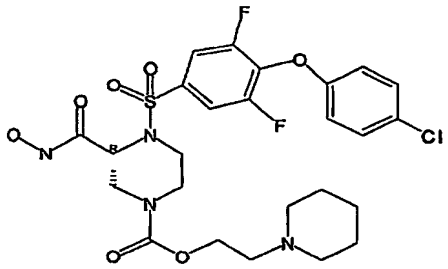
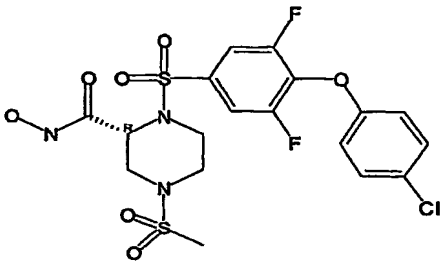
	(3R)-4-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-N~3~-hydroxy-N~1~-[2-(1-pyrrolidinyl)ethyl]-1,3-piperazinedicarboxamide,
	2-methoxyethyl (3R)-4-{[4-(4-cyanophenoxy)-3-fluorophenyl]sulfonyl}-3-[(hydroxyamino)carbonyl]-1-piperazinecarboxylate,
	2-methoxyethyl (3R)-4-{[6-(3-fluorophenyl)-3-pyridinyl]sulfonyl}-3-[(hydroxyamino)carbonyl]-1-piperazinecarboxylate,

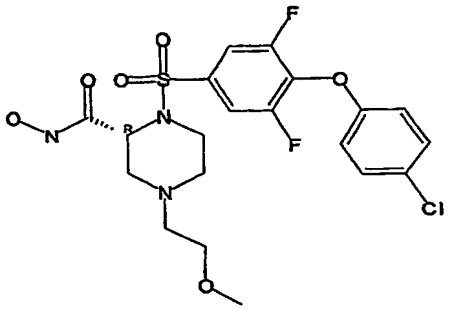
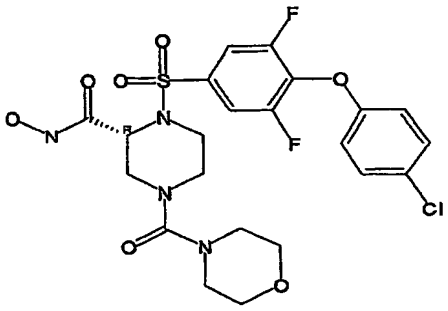
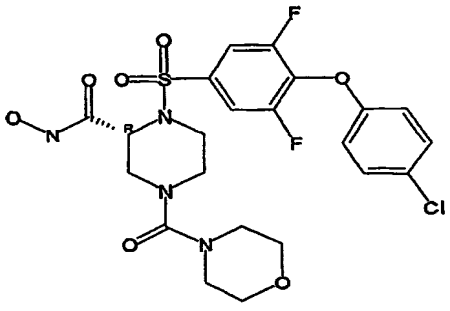
	2-(1-pyrrolidinyl)ethyl (3R)-4-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-3-[(hydroxyamino)carbonyl]-1-piperazinecarboxylate,
	(2R)-1-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-N-hydroxy-4-[2-(methylamino)-2-oxoethyl]-2-piperazinecarboxamide,
	(2R)-1-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-4-[2-(dimethylamino)-2-oxoethyl]-N-hydroxy-2-piperazinecarboxamide,

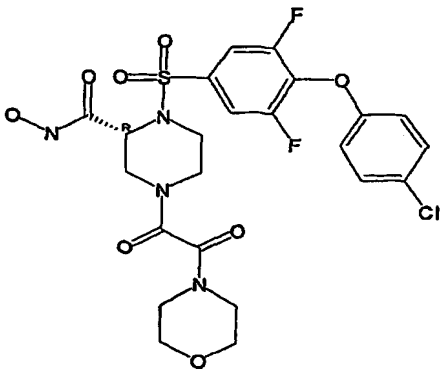
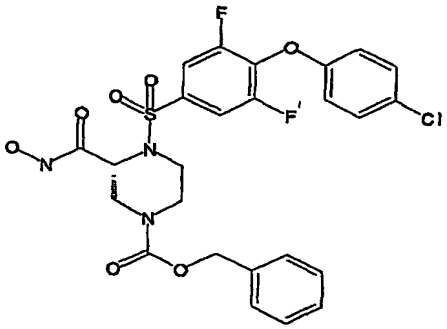
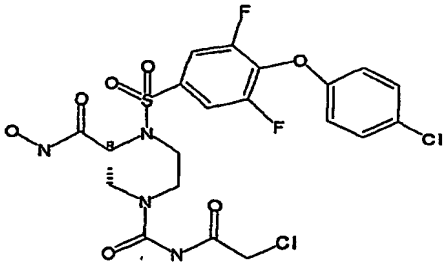
	(2R)-1-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-N-hydroxy-4-(1-pyrrolidinylacetyl)-2-piperazinecarboxamide,
	1-methyl-4-piperidinyl (3R)-4-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-3-[(hydroxyamino)carbonyl]-1-piperazinecarboxylate,
	2-methoxyethyl (3R)-4-{[6-(4-fluorophenoxy)-3-pyridinyl]sulfonyl}-3-[(hydroxyamino)carbonyl]-1-piperazinecarboxylate,

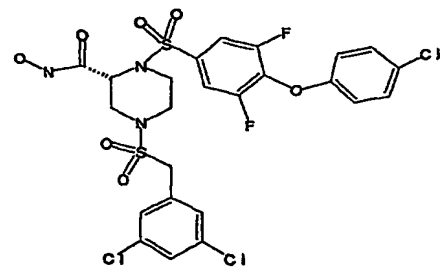
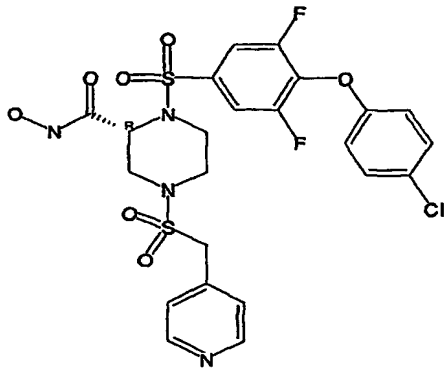
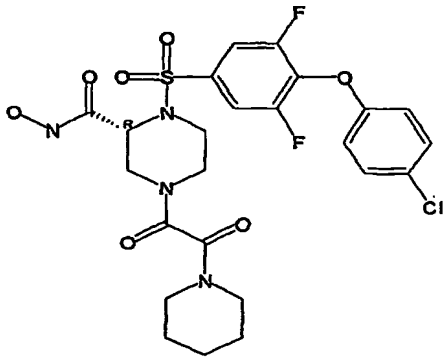
	2-methoxyethyl (3R)-3-[(hydroxyamino)carbonyl]-4-{[6-(5,6,7,8-tetrahydro-2-naphthalenyloxy)-3-pyridinyl]sulfonyl}-1-piperazinecarboxylate,
	{(3S)-4-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-3-[(hydroxyamino)carbonyl]-1-piperazinyl}acetic acid,
	ethyl 4-(2-{(3R)-4-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-3-[(hydroxyamino)carbonyl]-1-piperazinyl}-2-oxoethyl)-1-piperazinecarboxylate,

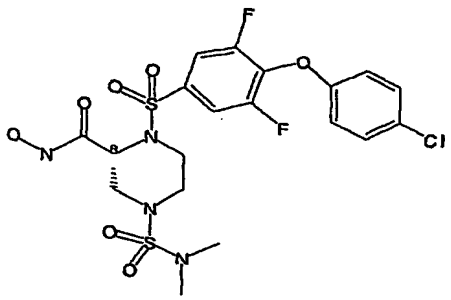
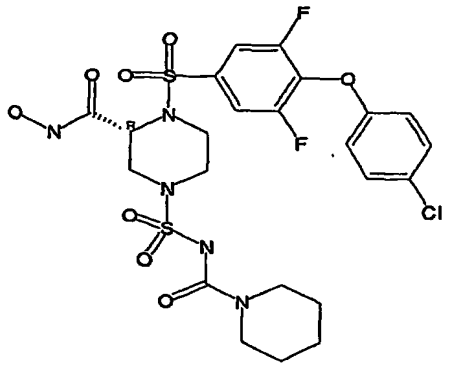
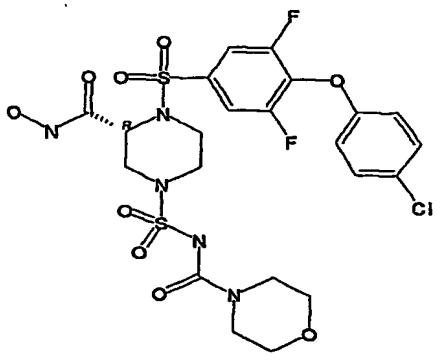
	(2R)-1-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-N-hydroxy-4-[(4-methyl-1-piperazinyl)acetyl]-2-piperazinecarboxamide,
	(2R)-1-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-N-hydroxy-4-(4-morpholinylacetyl)-2-piperazinecarboxamide,
	(2S)-4-allyl-1-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-N-hydroxy-2-piperazinecarboxamide,

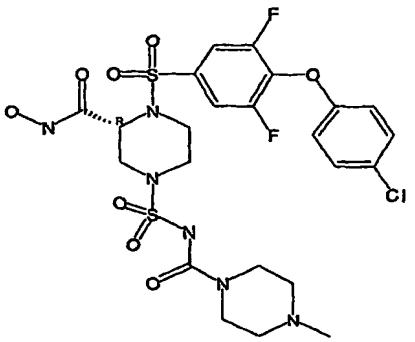
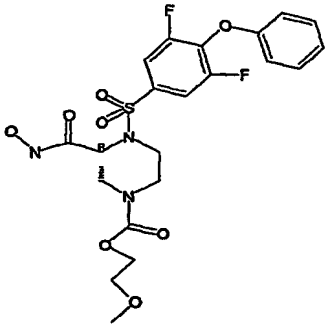
	(2R)-1-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-N-hydroxy-4-(1-piperidinylacetyl)-2-piperazinecarboxamide,
	2-(1-piperidinyl)ethyl (3R)-4-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-3-[(hydroxyamino)carbonyl]-1-piperazinecarboxylate,
	(2R)-1-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-N-hydroxy-4-(methylsulfonyl)-2-piperazinecarboxamide,

	(2R)-1-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-N-hydroxy-4-(2-methoxyethyl)-2-piperazinecarboxamide,
	(2R)-1-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-N-hydroxy-4-(4-morpholinylcarbonyl)-2-piperazinecarboxamide,
	(2R)-1-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-N-hydroxy-4-(4-morpholinylcarbonyl)-2-piperazinecarboxamide,

	(2R)-1-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-N-hydroxy-4-[4-morpholinyl(oxo)acetyl]-2-piperazinecarboxamide,
	benzyl (3R)-4-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-3-[(hydroxyamino)carbonyl]-1-piperazinecarboxylate,
	(3R)-N~1~-(chloroacetyl)-4-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-N~3~-hydroxy-1,3-piperazinedicarboxamide,

	(2S)-1-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-4-[(3,5-dichlorobenzyl)sulfonyl]-N-hydroxy-2-piperazinecarboxamide,
	(2R)-1-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-N-hydroxy-4-[(4-pyridinylmethyl)sulfonyl]-2-piperazinecarboxamide,
	(2R)-1-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-N-hydroxy-4-[oxo(1-piperidinyl)acetyl]-2-piperazinecarboxamide,

	(2R)-1-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-4-[(dimethylamino)sulfonyl]-N-hydroxy-2-piperazinecarboxamide,
	(2R)-1-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-N-hydroxy-4-{[(1-piperidinylcarbonyl)amino]sulfonyl}-2-piperazinecarboxamide,
	(2R)-1-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-N-hydroxy-4-{[(4-morpholinylcarbonyl)amino]sulfonyl}-2-piperazinecarboxamide,

	(2R)-1-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-N-hydroxy-4-({[(4-methyl-1-piperazinyl)carbonyl]amino}sulfonyl)-2-piperazinecarboxamide, and
	2-methoxyethyl (3R)-4-[(3,5-difluoro-4-phenoxyphenyl)sulfonyl]-3-[(hydroxyamino)carbonyl]-1-piperazinecarboxylate.

[0022] The following paragraphs provide definitions of the various chemical moieties that make up the compounds of the invention and are intended to apply uniformly throughout the specification and claims unless expressly stated otherwise.

[0023] The term alkyl refers to a univalent C_1 to C_6 saturated straight, branched, or cyclic alkane moiety and specifically includes methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, cyclopentyl, isopentyl, neopentyl, hexyl, isohexyl, cyclohexyl, 3-methylpentyl, 2,2-dimethylbutyl, and 2,3-dimethylbutyl. The alkyl group can be optionally substituted with any appropriate group, including but not limited to R^3 or one or more moieties selected from the group consisting of halo, hydroxyl, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate, either unprotected, or protected as necessary, as known to those

killed in the art or as taught, for example, in Greene, *et al.*, "Protective Groups in Organic Synthesis," John Wiley and Sons, Second Edition, 1991.

[0024] The term alkoxy refers to an alkyl moiety having a terminal –O- with a free valence, e.g., CH_3CH_2-O-;

[0025] The term alkenyl refers to a univalent C_2-C_6 straight, branched, or in the case of C_{5-6}, cyclic hydrocarbon with at least one double bond.

[0026] The term alkynyl refers to a univalent C_2-C_6 straight, branched, or in the case of C_{5-6}, cyclic hydrocarbon with at least one triple bond.

[0027] The term aryl refers to a univalent phenyl (preferably), biphenyl, or napthyl. The aryl group can be optionally substituted with any suitable group, including but not limited to one or more moieties selected from the group consisting of halo, hydroxyl, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate, either unprotected, or protected as necessary, as known to those skilled in the art, for example, as taught in Greene, et al., "Protective Groups in Organic Synthesis," John Wiley and Sons, Second Edition, 1991).

[0028] The term heteroatom means O, S, or N.

[0029] The term heterocycle refers to a cyclic alkyl or alkenyl moiety as defined above wherein one or more ring carbon atoms is replaced with a heteroatom.

[0030] The term halo refers to chloro, fluoro, iodo, or bromo.

[0031] The term unsaturated or mono- or poly-unsaturated C_3-C_{14}-mono- or fused polycyclic hydrocarbyl optionally containing one or two annular heteroatoms per ring refers to an aromatic or non-aromatic hydrocarbyl of 3 - 14 carbons forming a single ring or multiple fused rings and having one or more double and/or triple bonds and up to two heteroatoms as ring members of each ring. A non-exhaustive list of illustrative examples include cyclopentenyl, 2,4-cyclopentadienyl, phenyl, indenyl, naphthyl, 5,6,7,8-tetrahydro-2-naphthyl, phenanthryl, furyl, thienyl, pyranyl, isobenzofuranyl, chromenyl, pyrrolyl, imidazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl, oxadiazolyl, indolyl, quinolyl, carbazolyl, acrydinyl, furazanyl, etc. Specifically excluded from the scope of this term are compounds having adjacent annular O and/or S atoms.

[0032] A moiety that is substituted is one in which one or more hydrogens have been independently replaced with another chemical substituent. As a non-limiting example, substituted phenyls in-

lude 2-flurophenyl, 3,4-dichlorophenyl, 3-chloro-4-fluoro-phenyl, 2-fluor-3-propylphenyl. As another non-limiting example, substituted n-octyls include 2,4 dimethyl-5-ethyl-octyl and 3-cyclopentyl-octyl.

[0033] The term "pharmaceutically acceptable salts, esters, amides, and prodrugs" as used herein refers to those carboxylate salts, amino acid addition salts, esters, amides, and prodrugs of the compounds of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of patients without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. The term "salts" refers to the relatively non-toxic, inorganic and organic acid addition salts of compounds of the present invention. These salts can be prepared in situ during the final isolation and purification of the compounds or by separately reacting the purified compound in its free base form with a suitable organic or inorganic acid and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate mesylate, glucoheptonate, lactobionate and laurylsulphonate salts, and the like. These may include cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, and the like, as well as non-toxic ammonium, quaternary ammonium and amine cations including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. The compounds can also be administered as pharmaceutically acceptable quaternary salts known by those skilled in the art, which specifically include the quaternary ammonium salt of the formula -NR + Z-, wherein R is hydrogen, alkyl, or benzyl, and Z is a counterion, including chloride, bromide, iodide, -O-alkyl, toluenesulfonate, methylsulfonate, sulfonate, phosphate, or carboxylate (such as benzoate, succinate, acetate, glycolate, maleate, malate, citrate, tartrate, ascorbate, benzoate, cinnamoate, mandeloate, benzyloate, and diphenylacetate). (See, for example, S. M. Berge, et al., "Pharmaceutical Salts," J. Pharm. Sci., 1977;66:1-19 which is incorporated herein by reference.)

[0034] Examples of pharmaceutically acceptable, non-toxic esters of the compounds of this invention include C_1 -C_6 alkyl esters wherein the alkyl group is a straight or branched chain. Acceptable esters also include C_5 -C_7 cycloalkyl esters as well as arylalkyl esters such as, but not limited to benzyl, C_1 -C_4 alkyl esters are preferred. Esters of the compounds of the present invention may be prepared according to conventional methods.

[0035] Examples of pharmaceutically acceptable, non-toxic amides of the compounds of this invention include amides derived from ammonia, primary C_1 -C_6 alkyl amines and secondary C_1 -C_6 dialkyl amines wherein the alkyl groups are straight or branched chain. In the case of secondary amines the amine may also be in the form of a 5- or 6-membered heterocycle containing one nitrogen atom. Amides derived from ammonia, C_1 -C_3 alkyl primary amines, and C_1 -C_2 dialkyl secondary amines are preferred. Amides of the compounds of the invention may be prepared according to conventional methods.

[0036] The term "prodrug" refers to compounds that are rapidly transformed in vivo to yield the parent compound of the above formulae, for example, by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

[0037] In addition, the compounds of the present invention can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present invention.

[0038] The compounds of the present invention may also exist in different stereoisomeric forms by virtue of the presence of one or more asymmetric centers in the compound. The present invention contemplates all stereoisomeric forms of the compounds as well as mixtures thereof, including racemic mixtures. Individual stereoisomers may be obtained, if desired by methods known in the art as, for example, the separation of stereoisomers in chiral chromatographic columns.

[0039] The term pharmaceutically active derivative refers to any compound that upon administration to the recipient, is capable of providing directly or indirectly, the compounds disclosed herein.

[0040] In another embodiment, the invention comprises a pharmaceutical composition comprising a compound as described in any of paragraphs [0011] – [0021] and a pharmaceutically acceptable carrier.

[0041] The active compound is included in the pharmaceutically acceptable carrier or diluent in an amount sufficient to deliver to a patient a therapeutically effective amount without causing serious toxic effects in the patient treated. A preferred dose of the active compound for all of the above-

mentioned conditions is in the range from about 0.01 to 300 mg/kg, preferably 0.1 to 100 mg/kg per day, more generally 0.5 to about 25 mg per kilogram body weight of the recipient per day. A typical topical dosage will range from 0.01–3% wt/wt in a suitable carrier. The effective dosage range of the pharmaceutically acceptable derivatives can be calculated based on the weight of the parent compound to be delivered. If the derivative exhibits activity in itself, the effective dosage can be estimated as above using the weight of the derivative, or by other means known to those skilled in the art.

[0042] The methods of the invention comprise administration to a mammal (preferably human) suffering from forms of cancer, arthritis, and diseases related to angiogenesis in which ADAM-10 plays a critical role a pharmaceutical composition according to the invention in an amount sufficient to alleviate the condition. The compound is conveniently administered in any suitable unit dosage form, including but not limited to one containing 1 to 3000 mg, preferably 5 to 500 mg of active ingredient per unit dosage form. A oral dosage of 1–500, preferably 10-250, more preferably 25-250 mg is usually convenient.

[0043] The active ingredient should be administered to achieve peak plasma concentrations of the active compound of about 0.001–30 μM, preferably about 0.01–10 μM. This may be achieved, for example, by the intravenous injection of a solution or formulation of the active ingredient, optionally in saline, or an aqueous medium or administered as a bolus of the active ingredient.

[0044] The concentration of active compound in the drug composition will depend on absorption, distribution, inactivation, and excretion rates of the drug as well as other factors known to those of skill in the art. It is to be noted that dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed composition. The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at varying intervals of time.

[0045] Oral compositions will generally include an inert diluent or an edible carrier. They may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets,

oches, or capsules. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition.

The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a dispersing agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterores; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring. When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials which modify the physical form of the dosage unit, for example, coatings of sugar, shellac, or enteric agents. *See generally* "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, PA.

[0046] The active compound or pharmaceutically acceptable salt or derivative thereof can be administered as a component of an elixir, suspension, syrup, wafer, chewing gum or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

[0047] The active compound or pharmaceutically acceptable derivatives or salts thereof can also be mixed with other active materials that do not impair the desired action, or with materials that supplement the desired action, such as antibiotics, antifungals, other anti-inflammatories, or antiviral compounds.

[0048] Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerin, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parental preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

[0049] If administered intravenously, preferred carriers are physiological saline or phosphate buffered saline (PBS).

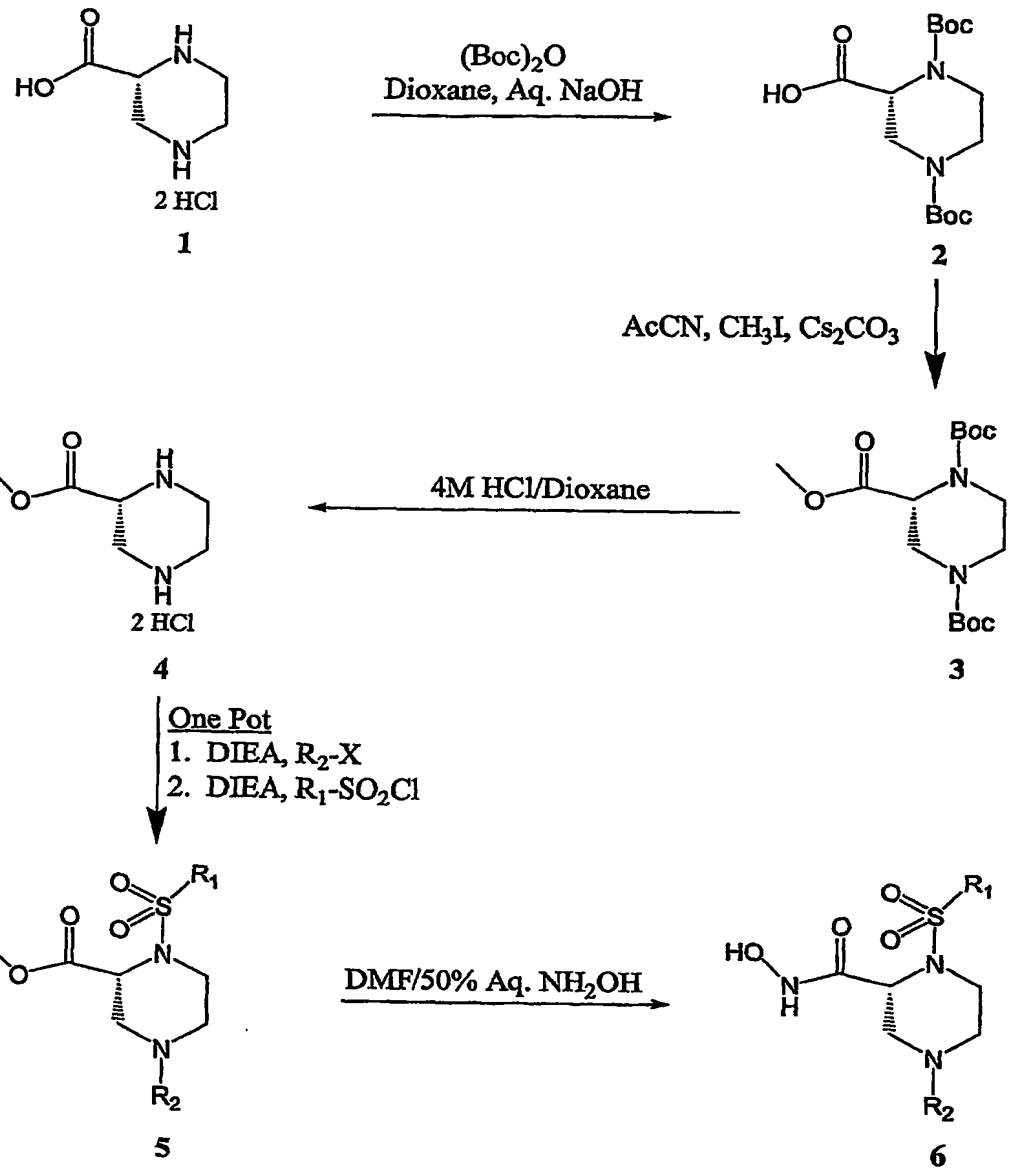
[0050] In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation (CA) and Gilford Pharmaceuticals (Baltimore, Md.). Liposomal suspensions may also be pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811 (which is incorporated herein by reference in its entirety). For example, liposome formulations may be prepared by dissolving appropriate lipid(s) (such as stearoyl phosphatidyl ethanolamine, stearoyl phosphatidylcholine, arachadoyl phosphatidylcholine, and cholesterol) in an inorganic solvent that is then evaporated, leaving behind a thin film of dried lipid on the surface of the container. An aqueous solution of the active compound or its monophosphate, diphosphate, and/or triphosphate derivatives are then introduced into the container. The container is then swirled by hand to free lipid material from the sides of the container and to disperse lipid aggregates, thereby forming the liposomal suspension.

Synthesis

[0051] The compounds of the invention can be made in accordance with the following general description and following the teachings provided in the Examples, below, and methods routine to those of ordinary skill in the art. The Examples are merely illustrative and are not intended to be limiting.

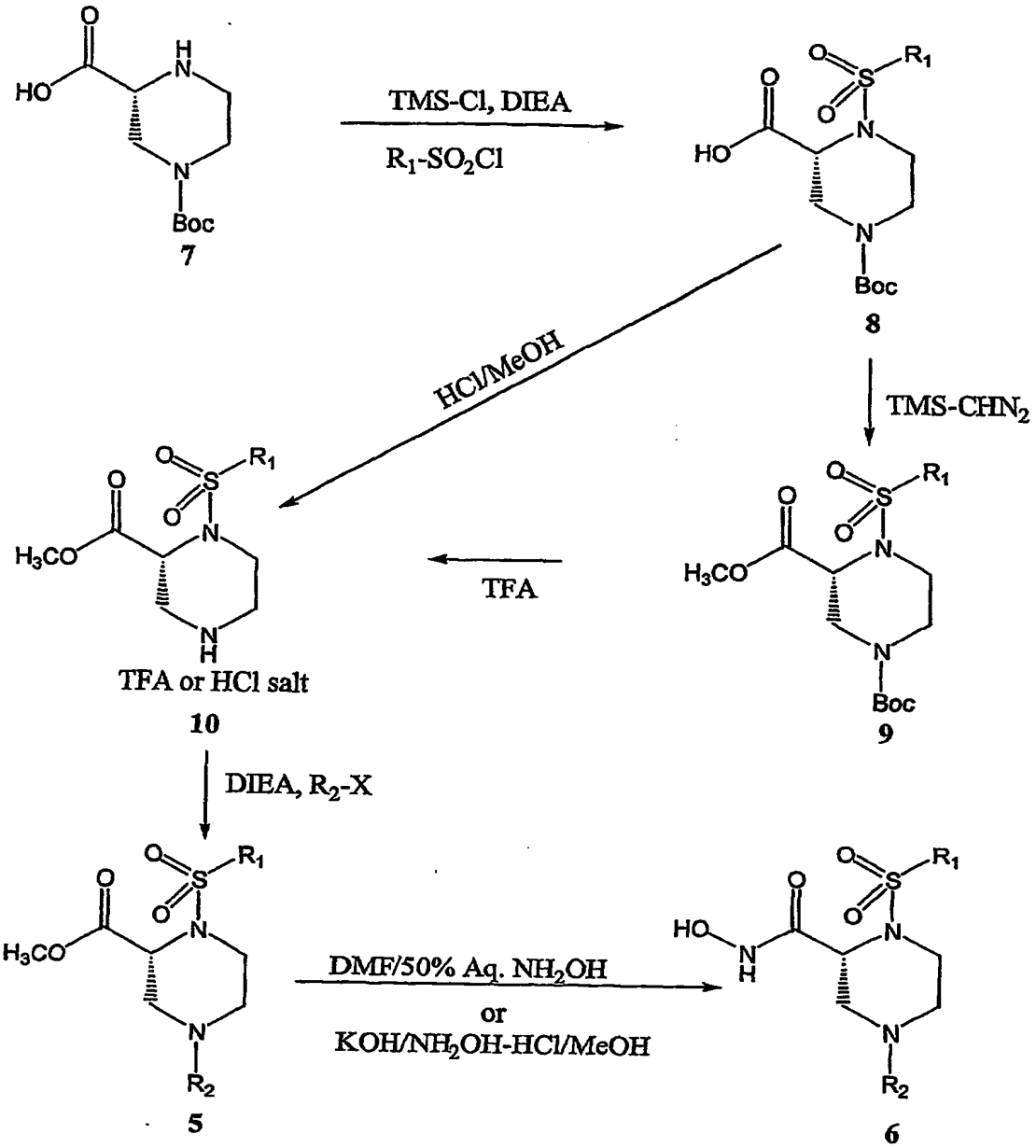
[0052] The N-hydroxy-1,4-disubstituted piperazine-2-(R)-carboxamides of the present invention can be synthesized using the methods described below. Method A begins with the reaction of piperazine-2-(R)-carboxylic acid dihydrochloride (**1**) with di-*tert*-butyl dicarbonate to yield the bis-Boc protected species **2**, which is esterified with methyl iodide in the presence of cesium carbonate to form methyl ester **3**. The Boc groups are then removed from **3** to yield the key piperazine dihydrochloride intermediate **4**.

METHOD A



[0053] In one pot, the N4 nitrogen of **4** is selectively acylated, carbamylated, sulfonylated, alkylated, etc., followed by sulfonylation of the N1 nitrogen to form the disubstituted piperazine **5**. Methyl ester **5** is then converted to the hydroxamate in a mixture of DMF and 50% aqueous hydroxylamine to give the desired N-hydroxy-1,4-disubstituted piperazine-2-(R)-carboxamide **6**.

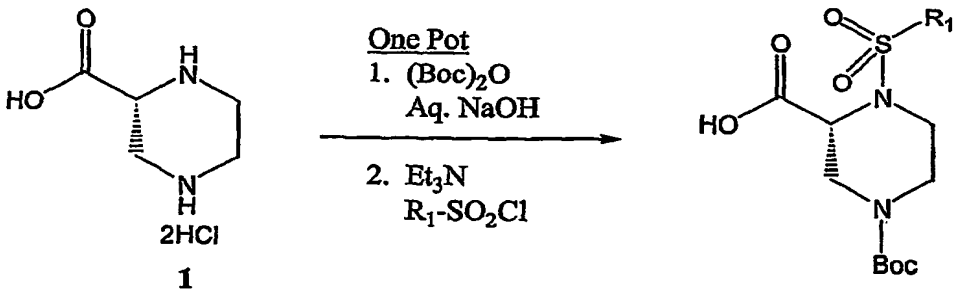
METHOD B



[0054] Method B begins with the sulfonylation of the N1 nitrogen of the mono-Boc protected piperazine-2-(R)-carboxylic acid **7** through the use of trimethylsilyl chloride and the appropriate sulfonyl chloride to form intermediate **8**. Compound **8** is then esterifed with TMS-diazomethane to form methyl ester **9**, followed by deprotection of the Boc group with TFA to form the TFA salt of **10**. Alternatively, compound **8** can be simultaneously esterified and Boc-deprotected using HCl in methanol to form the HCl salt of **10**. The N4 nitrogen of **10** is acylated, carbamylated, sulfonylated, alkylated,

etc. to form methyl ester **5**, which is converted to the hydroxamate using a mixture of DMF and 50% aqueous hydroxylamine as described above or, alternatively, by treatment with hydroxylamine under basic conditions (KOH in MeOH).

METHOD C



1 **8**

[0055] Method C begins with the one pot synthesis of the the disubstituted piperazine-2-(R)-carboxylic acid **8** from the dihydrochloride **1**. First, under Schotten-Baumann conditions, the N4 nitrogen of **1** is selectively Boc-protected, followed by the addition of triethylamine and the appropriate sulfonyl chloride to sulfonylate the N1 nitrogen to form **8**. From intermediate **8**, the desired hydroxamate **6** is formed as previously described in Method B.

EXAMPLES

Example 1

N-Hydroxy-1-[4-(4-fluorophenoxy)-phenyl)]sulfonyl-4-(4-morpholinylcarbonyl)piperazine-2-(R)-carboxamide

(Method A)

Step 1 – Formation of 1,4-di-*tert*-butoxycarbonylpiperazine-2-(R)-carboxylic acid

[0056] Piperazine-2-(R)-carboxylic acid dihydrochloride(16.6g, 82mmol) and dioxane (120ml) were combined and cooled in an icebath. 5N NaOH (60ml, 300mmol) was added, followed by $(Boc)_2O$ (41.8g, 191mmol). The reaction mixture was allowed to warm to room temperature with stirring over several hours, then concentrated *in vacuo*. The resulting aqueous mixture was washed with Et_2O (3x), cooled in an icebath, acidified to pH 2-3 with concentrated HCl and extracted with EtOAc (3x). Combined EtOAc extractions were washed with water (1x), saturated NaCl (1x), dried (Na_2SO_4), and concentrated *in vacuo* to give 1,4-di-*tert*-butoxycarbonylpiperazine-2-(R)-carboxylic acid as a white solid (27.0g, 100%). LC/MS Calcd for $[M-H]^-$ 329.2, found 329.2.

Step 2 – Formation of methyl 1,4-di-tert-butoxycarbonylpiperazine-2-(R)-carboxylate

[0057] 1,4-Di-*tert*-butoxycarbonylpiperazine-2-(R)-carboxylic acid (70g, 212 mmol) was dissolved in acetonitrile (1.3L). Cs_2CO_3 (110g, 340mmol) was added and the mixture stirred for 30 minutes at room temperature before the addition of methyl iodide (28ml, 450mmol). The reaction mixture was stirred at room temperature overnight, solids were filtered and the filtrate concentrated *in vacuo*. The resulting oil was dissolved in EtOAc and any insoluble material filtered. The filtrate was concentrated *in vacuo* to give methyl 1,4-di-*tert*-butoxycarbonylpiperazine-2-(R)-carboxylate (69g, 95%). LC/MS Calcd for $[M+H]^+$ 345.2, found 145.1 (-Boc X 2).

Step 3 – Formation of methyl piperazine-2-(R)-carboxylate dihydrochloride

[0058] Methyl 1,4-di-*tert*-butoxycarbonylpiperazine-2-(R)-carboxylate (2.9g, 8.5mmol) was dissolved in 4M HCl in dioxane (30ml) and stirred at room temperature for 30-60 minutes, forming a thick white precipitate. The reaction mixture was concentrated *in vacuo* and the resulting white solid dried under high vacuum to give methyl piperazine-2-(R)-carboxylate dihydrochloride (1.9g, 100%). LC/MS Calcd for $[M+H]^+$ 145.1, found 145.1.

Step 4 – Formation of methyl 1-[4-(4-fluorophenoxy)phenyl)]sulfonyl-4-(4-morpholinylcarbonyl)piperazine-2-(R)-carboxylate

[0059] Methyl piperazine-2-(R)-carboxylate dihydrochloride (676mgs, 3.1mmol) was dissolved in CH_2Cl_2 (7mls) and DIEA (2.1mls, 12.4mmol) and cooled in an icebath. Morpholinecarbonyl chloride (450mgs, 3.0mmol) dissolved in methylene chloride (2.5mls) was added dropwise with stirring. After addition was complete, the reaction mixture was allowed to warm to room temperature and stirred for an additional 2-3hrs. Additional DIEA (0.6mls, 3.4mmol) was added, followed by 4-(4-fluorophenoxy)phenylsulfonyl chloride (904mg, 3.1mmol) and the reaction mixture stirred at room temperature overnight. The reaction mixture was concentrated *in vacuo* and the resulting residue redissolved in EtOAc and washed with water (1x), 1.0N HCl (2x), dried (Na_2SO_4), concentrated *in vacuo* and purified by flash chromatography (3:1 EtOAc:hexanes) to give methyl 1-[4-(4-fluorophenoxy)phenyl)]sulfonyl-4-(4-morpholinylcarbonyl)piperazine-2-(R)-carboxylate (1.11g, 70%). LC/MS Calcd for $[M+H]^+$ 508.1, found 508.1.

Step 5 – Formation of N-hydroxy-1-[4-(4-fluorophenoxy)phenyl)]sulfonyl-4-(4-morpholinylcarbonyl)piperazine-2-(R)-carboxamide

[0060] Methyl 1-[4-(4-fluorophenoxy)phenyl)]sulfonyl-4-(4-morpholinylcarbonyl)piperazine-2-(R)-carboxylate (1.11g, 2.2mmol) was dissolved in DMF (17mls) to which was added 50% aqueous NH_2OH (20mls) and the reaction mixture stirred at room temperature overnight. The reaction mixture was poured into cold 1.0N HCl (100-120mls) and extracted with EtOAc (4x). The combined EtOAc extractions were washed with 10% aqueous LiCl (4x), saturated NaCl (1x), dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was purified by flash chromatography (EtOAc) and the resulting pure oil was dissolved in 1:1 acetonitrile:water and lyophilized to give N-hydroxy-1-[4-(4-fluorophenoxy)phenyl)]sulfonyl-4-(4-morpholinylcarbonyl)piperazine-2-(R)-carboxamide as a white solid (659mg, 59%). LC/MS Calcd for $[M+H]^+$ 509.1, found 509.1. ^{1}HNMR (400MHz, CD_3OD): δ 7.69 (d, 2H, *J*=9.2 Hz), 7.04 (m, 4H), 6.95 (d, 2H, *J*=9.2 Hz), 4.30 (m, 1H), 3.76 (m, 1H), 3.50 (m, 7H), 3.10 (m, 4H), 2.90 (dd, 1H, *J*=13.2, 4.4 Hz), 2.72 (m, 1H).

Example 2

N-Hydroxy-1-[4-(4-fluorophenoxy)-3,5-difluorophenyl)] sulfonyl-4-(ethoxycarbonyl)piperazine-2-(R)-carboxamide

(Method B)

Step 1 – Formation of 1-[4-(4-fluorophenoxy)-3,5-difluorophenyl)]sulfonyl-4-boc-piperazine-2-(R)-carboxylic acid

[0061] 4-Boc-piperazine-2-(R)-carboxylic acid (933mg, 4.05mmol), CH_2Cl_2 (12ml), DMF (6ml), and DIEA (2.5ml, 14.3mmol) were combined under N_2. TMS-Cl (810µl, 6.38mmol) was added slowly and the mixture stirred at room temperature for approximately 2 hrs. 4-(4-fluorophenoxy)-3,5-difluorophenyl)]sulfonyl chloride (1.43g, 4.43mmol) dissolved in a minimum of CH_2Cl_2 was added and the mixture stirred at room temperature for another 2 hrs. The reaction mixture was diluted with EtOAc and washed with 0.5N HCl (3x), sat'd NaCl (1x), dried (Na_2SO_4), and concentrated *in vacuo*. The resulting crude oil was purified by flash chromatography (6:4 hexanes:EtOAc + 1% AcOH) to give the desired product (1.37g, 65%). LC/MS Calcd for $[M+H]^+$ 517.1, found 417.0 (-Boc).

Step 2 – Formation of methyl 1-[4-(4-fluorophenoxy)-3,5-difluorophenyl)]sulfonyl-4-boc-piperazine-2-(R)-carboxylate

[0062] 1-[4-(4-fluorophenoxy)-3,5-difluorophenyl)]sulfonyl-4-boc-piperazine-2-(R)-carboxylic acid (1.37g, 2.65mmol) was dissolved in CH_2Cl_2 (40ml) and MeOH (10ml). A mixture of 2M TMS-CHN_2 in hexanes (2.5ml, 5mmol) and CH_2Cl_2 (10ml) was added dropwise with stirring and the reaction followed by TLC. Upon completion of the reaction, AcOH (1.0ml) was added dropwise with stirring. The reaction mixture was further diluted with CH_2Cl_2 and washed with water (1x), saturated $NaHCO_3$ (2x), saturated NaCl (1x), dried ($MgSO_4$), and concentrated *in vacuo*. The crude oil was purified by flash chromatography (3:1 hexanes:EtOAc) to give the desired product (1.10g, 78%). LC/MS Calcd for $[M+H]^+$ 531.1, found 431.0 (-Boc).

Step 3 – Formation of methyl 1-[4-(4-fluorophenoxy)-3,5-difluorophenyl)]sulfonyl-piperazine-2-(R)-carboxylate TFA salt

[0063] Methyl 1-[4-(4-fluorophenoxy)-3,5-difluorophenyl)]sulfonyl-4-boc-piperazine-2-(R)-carboxylate (1.10g, 2.07mmol) was dissolved in a minimum of CH_2Cl_2 to which was added neat TFA (10ml). The mixture was stirred at room temperature for approximately 30min, concentrated *in vacuo*, further dried for several hours under high vacuum and used without further purification. LC/MS Calcd for $[M+H]^+$ 431.1, found 431.0.

Step 4 – Formation of methyl 1-[4-(4-fluorophenoxy)-3,5-difluorophenyl)]sulfonyl-4-(ethoxycarbonyl) piperazine-2-(R)-carboxylate

[0064] To a mixture of methyl 1-[4-(4-fluorophenoxy)-3,5-difluorophenyl)]sulfonyl-piperazine-2-(R)-carboxylate TFA salt (344mg, 0.63mmol), CH_2Cl_2 (10ml), and DIEA (250µl, 1.43mmol) under N_2 was added ethyl chloroformate (65µl, 0.68mmol). The mixture was stirred under N_2 at room temperature for 1.5 hrs, then washed with 1.0N HCl (2x), saturated NaCl (1x), dried (Na_2SO_4), and concentrated *in vacuo*. The crude residue was purified by flash chromatography (3:1 hexanes:EtOAc) to give the desired product (218mgs, 69%). LC/MS Calcd for $[M+H]^+$ 503.1, found 503.0.

Step 5 – Formation of N-hydroxy-1-[4-(4-fluorophenoxy)-3,5-difluorophenyl)]sulfonyl-4-(ethoxycarbonyl) piperazine-2-(R)-carboxamide

[0065] A 1.7M solution of NH_2OH in MeOH was prepared by mixing a solution of KOH (2.80g, 50.0mmol) in MeOH (7.0ml) with a hot solution of NH_2OH HCl salt (2.40g, 34.5mmol) in MeOH

12.0ml) and filtering the resulting solids after cooling to room temperature. Methyl 1-[4-(4-fluorophenoxy)-3,5-difluorophenyl)]sulfonyl-4-(ethoxycarbonyl)piperazine-2-(R)-carboxylate (218mg, 0.43mmol) was dissloved in the 1.7M NH_2OH in MeOH solution (4.0ml) and stirred at room temperature for 30-45 minutes. The reaction mixture was then diluted with 1.0N HCl and extracted with EtOAc (3x). Combined EtOAc extractions were washed with saturated NaCl (1x), dried (Na_2SO_4), and concentrated *in vacuo*. The resulting crude residue was purified by flash chromatography (1:1 EtOAc:hexanes) to give a colorless film which was lyophilized from 1:1 AcCN:H_2O to give the desired product as a white solid (136mg, 62%). LC/MS Calcd for $[M+H]^+$ 504.1, found 504.0. ^{1}HNMR (400MHz, CD_3OD): δ 7.58 (m, 2H), 7.03 (m, 4H), 4.27 (m, 2H), 4.07 (m, 3H), 3.75 (m, 2H), 3.30 (m, 1H), 3.06 (m, 1H), 1.22 (m, 3H).

Example 3

N-Hydroxy-1-[4-(4-cyanophenoxy)-3-fluorophenyl)]sulfonyl-4-(2-methoxy-1-ethoxycarbonyl)piperazine-2-(R)-carboxamide.

(Method C)

Step 1 – Formation of 1-[4-(4-cyanophenoxy)-3-fluorophenyl)]sulfonyl-4-boc-piperazine-2-(R)-carboxylic acid

[0066] Piperazine-2-(R)-carboxylic acid dihydrochloride (1.25g, 6.1mmol), dioxane (15mls) and water (6.0mls) were combined and cooled in an icebath. 9N NaOH (2.0mls, 18mmol) was added slowly with stirring, followed by $(Boc)_2O$ (1.35g, 6.2mmol). The reaction mixture was allowed to warm to room temperature and stirred for an additional 3-4 hrs. Et_3N (1.8mls, 13mmol) was added, followed by 4-cyanophenoxy-3-fluorophenylsulfonyl chloride (2.00g, 6.4mmol). The reaction mixture is stirred at room temperature for 1-2 hrs, then concentrated *in vacuo*. The resulting residue was partitioned between 1.0N HCl and EtOAc. Phases were separated and the aqueous phase was further extracted with EtOAc (2x). Combined EtOAc extractions were washed with 1.0N HCl (1x), saturated NaCl (1x), dried ($MgSO_4$), and concentrated *in vacuo*. The resulting residue is purified by flash chromatography (7:3 hexanes:EtOAc + 1% AcOH) to give the desired product (1.1g, 35%). LC/MS Calcd for $[M-H]^-$ 504.1, found 504.3.

Step 2

[0067] Methyl 1-[4-(4-cyanophenoxy)-3-fluorophenyl)]sulfonyl-4-boc-piperazine-2-(R)-carboxylate was made in the same manner as Example 2, step 2, except purification by flash chrmoatography was unnecessary. 1.10g recovered (97%). LC/MS Calcd for $[M+H]^+$ 520.1, found 420.1 (-Boc).

Step 3

[0068] Methyl 1-[4-(4-cyanophenoxy)-3-fluorophenyl)]sulfonyl-piperazine-2-(R)-carboxylate TFA salt was made in the same manner as Example 2, step 3. LC/MS Calcd for $[M+H]^+$ 420.1, found 420.2.

Step 4

[0069] Methyl 1-[4-(4-cyanophenoxy)-3-fluorophenyl)]sulfonyl-4-(2-methoxy-1-ethoxycarbonyl) piperazine-2-(R)-carboxylate was made in the same manner as Example 2, step 4. 438mgs recovered (83%). LC/MS Calcd for $[M+H]^+$ 522.1, found 522.2.

Step 5

[0070] N-Hydroxy-1-[4-(4-cyanophenoxy)-3-fluorophenyl)]sulfonyl-4-(2-methoxy-1-ethoxycarbonyl)piperazine-2-(R)-carboxamide was made in the same manner as Example 2, step 5. 46mg recovered (10%). LC/MS Calcd for $[M-H]^-$ 521.1, found 521.2. ^{1}HNMR (400MHz, CD_3OD): δ 7.73 (m, 3H), 7.65 (m, 1H), 7.34 (m, 1H), 7.19 (d, 2H, J=8.4 Hz), 4.29 (m, 2H), 4.14 (m, 3H), 3.74 (m, 2H), 3.55 (m, 2H), 3.33 (s, 3H), 3.25 (m, 1H), 3.04 (m, 1H).

Example 4

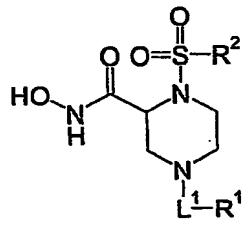
Enzyme Assays

[0071] mADAM-10 or hADAM-10 activity was measured as the ability to cleave a 10-residue peptide (DABCYL-Leu-Leu-Ala-Gln-Lys-*-Leu-Arg-Ser-Ser-Arg-EDANS). This peptide was based on the TNF-α cleavage site (Leu^{62}-Arg^{71}), however, we found that replacement of Ala^{76}-Val^{77} with Lys-Leu resulted in a peptide with a 5-fold greater affinity for ADAM-10 than the native TNF-α peptide. Enzyme was diluted to a final active concentration of 5nM in Buffer A (50mM HEPES 8.0, 100mM NaCl, 1mM CaCl2 and 0.01% NP-40). Serial dilutions for compounds were performed ranging from 100μM to 0.5nM using a Beckman Biomek 2000 in polypropylene plates (Greiner). 20 μl of enzyme solution was added to 10μl of compound in buffer A, and allowed to incubate for 15min in 384 well black, Greiner, microtiter plates (#781076). 20μl of substrate (12.5μM in Buffer A) was then added, result-

g in final reaction conditions of 2nM ADAM-10, 5 μM substrate, and compound concentrations ranging from 20uM to 0.1nM. The reaction was incubated for 2hr at RT, and fluorescence was measured at Ex355, Em460 on a Wallac Victor 2 fluorescence reader. For final analysis of potent inhibitors, a similar reaction was set up with a final active ADAM-10 concentration of 0.1nM. This reaction was incubated for 16hr at RT and fluorescence was read using identical conditions.

claim:

1. A compound of structural formula I:



I

and pharmaceutically acceptable salts, esters, amides, and prodrugs thereof wherein

L^1 is -C(O)-, -$S(O)_2$-, or -$(CH_2)_n$- wherein n is 0, 1, 2, or 3;

R^1 is -OR^{11}, -$(CH_2)_nR^{11}$, -$C(O)R^{11}$, or -$NR^{12}R^{13}$;

R^{11}, R^{12}, and R^{13} independently are

d) R^{50};

e) saturated or mono- or poly- unsaturated C_5-C_{14}-mono- or fused poly- cyclic hydrocarbyl, optionally containing one or two annular heteroatoms per ring and optionally substituted with one or two R^{50} substituents;

f) C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, or -C(O)H, each of which is optionally substituted with one, two or three substituents independently selected from R^{50} and saturated or mono- or poly- unsaturated C_5-C_{14}-mono- or fused poly- cyclic hydrocarbyl, optionally containing one or two annular heteroatoms per ring and optionally substituted with one, two or three R^{50} substituents;

or R^{12} and R^{13} together with the N to which they are covalently bound, a C_5-C_6 heterocycle optionally containing a second annular heteroatom and optionally substituted with one or two R^{50} substituents;

R^2 is R^{21}-L^2-R^{22};

R^{21} is saturated or mono- or poly- unsaturated C_5-C_{14}-mono- or fused poly- cyclic hydrocarbyl, optionally containing one or two annular heteroatoms per ring and optionally substituted with one, two, or three R^{50} substituents;

L^2 is -O-, -C(O)-, -CH_2-, -NH-, -$S(O_2)$- or a direct bond;

R^{22} is saturated or mono- or poly- unsaturated C_5-C_{14}-mono- or fused poly- cyclic hydrocarbyl, optionally containing one or two annular heteroatoms per ring and optionally substituted with one, two, or three R^{50} substituents; and

R^{50} is R^{51}-L^3-$(CH_2)_n$-;

L^3 is -O-, -NH-, -S-, -C(O)-, -C(O)O-, -C(O)NH-, -OC(O)-, -NHC(O)-, or a direct bond;

R^{51} is -H, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, halo, -OH, $-NH_2$, -SH, $-CO_2H$, -CN, $-NO_2$, or $-SO_3H$;

provided that an O or S is not singly bonded to another O or S.

2. The compound according to claim 1 wherein L^1 is -C(O)-.

3. The compound according to claim 2 wherein R^1 is $-OR^{11}$.

4. The compound according to claim 3 wherein R^1 is C_1-C_6-alkoxy-C_1-C_6-alkoxy.

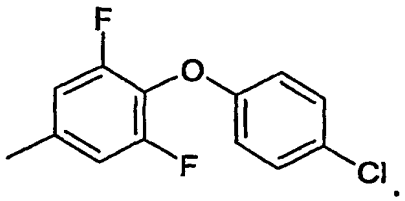
5. The compound according to claim 4 wherein R^1 is methoxyethoxy.

6. The compound according to claim 1 wherein L^1 is $-S(O)_2$-

7. The compound according to claim 1 wherein R^2 is phenoxyphenyl wherein each phenyl is optionally substituted with one or two R^{50} substituents.

8. The compound according to claim 7 wherein the R^{50} substituents are halo.

9. The compound according to claim 8 wherein R^2 is:

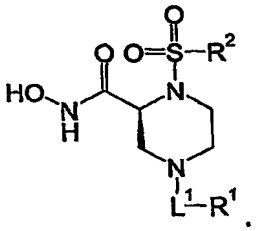


10. The compound according to claim 1 wherein the saturated or mono- or poly- unsaturated C_5-C_{14}-mono- or fused poly- cyclic hydrocarbyl containing one or two annular heteroatoms per ring are selected from the group consisting of morpholinyl, piperazinyl, homopiperazinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, furyl, thienyl, pyranyl, isobenzofuranyl, chromenyl, pyrrolyl, imida-

zolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl, oxadiazolyl, indolyl, quinolinyl, carbazolyl, acrydinyl, and furazanyl, optionally substituted with one or two R^{50} substituents.

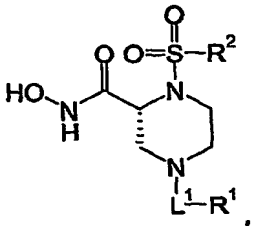
11. The compound according to claim 1 wherein R^{12} and R^{13}, together with the N to which they are covalently bound, form a heterocycle selected from the group consisting of morpholinyl, piperazinyl, homopiperazinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, pyrrolyl, imidazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl, oxadiazolyl, indolyl, quinolinyl, carbazolyl, acrydinyl, and furazanyl, optionally substituted with one or two R^{50} substituents.

12. The compound according to claim 1 having the stereochemistry of structure **II**:



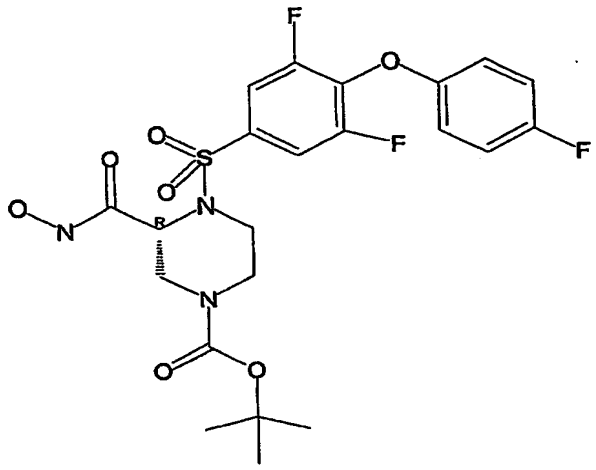
II

13. The compound according to claim 1 having the stereochemistry of structure **III**:

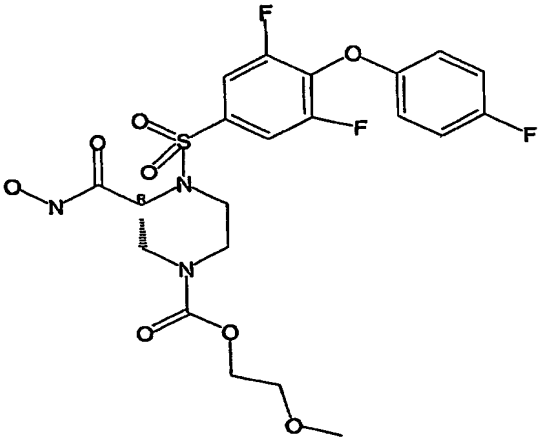


III

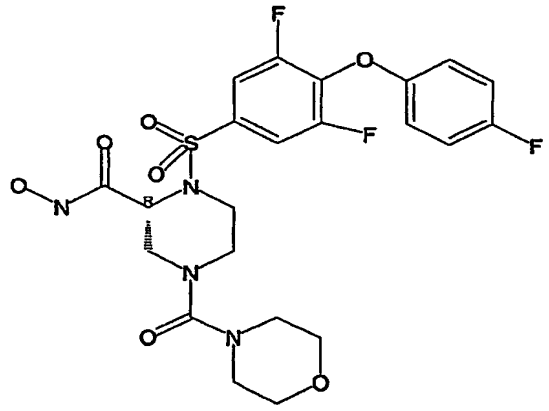
14. The compound according to claim 1 selected from the group consisting of:



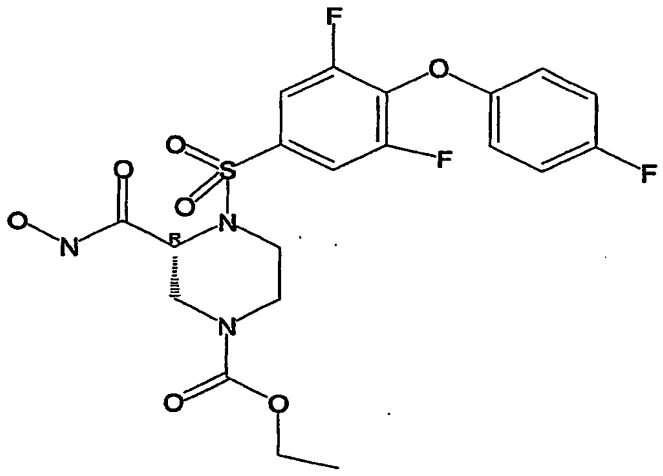
tert-butyl (3R)-4-{[3,5-difluoro-4-(4-fluorophenoxy)phenyl]sulfonyl}-3-[(hydroxyamino)carbonyl]-1-piperazinecarboxylate,



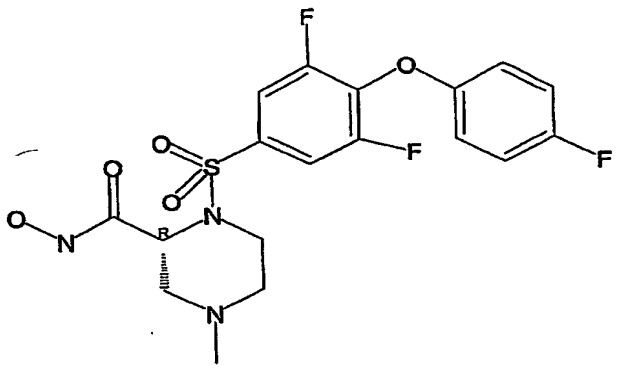
2-methoxyethyl (3R)-4-{[3,5-difluoro-4-(4-fluorophenoxy)phenyl]sulfonyl}-3-[(hydroxyamino)carbonyl]-1-piperazinecarboxylate,



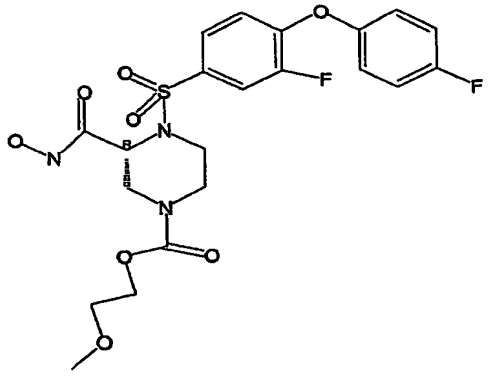
(2R)-1-{[3,5-difluoro-4-(4-fluorophenoxy)phenyl]sulfonyl}-N-hydroxy-4-(4-morpholinylcarbonyl)-2-piperazinecarboxamide,



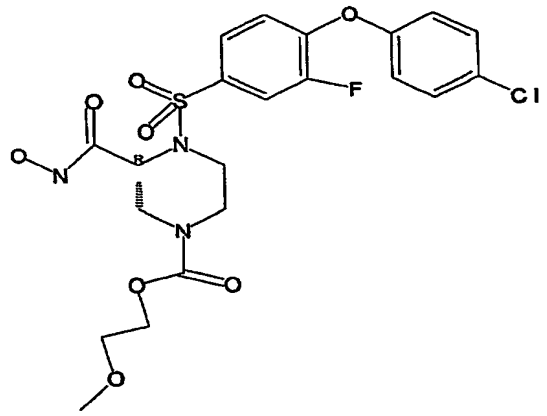
ethyl (3R)-4-{[3,5-difluoro-4-(4-fluorophenoxy)phenyl]sulfonyl}-3-[(hydroxyamino)carbonyl]-1-piperazinecarboxylate,



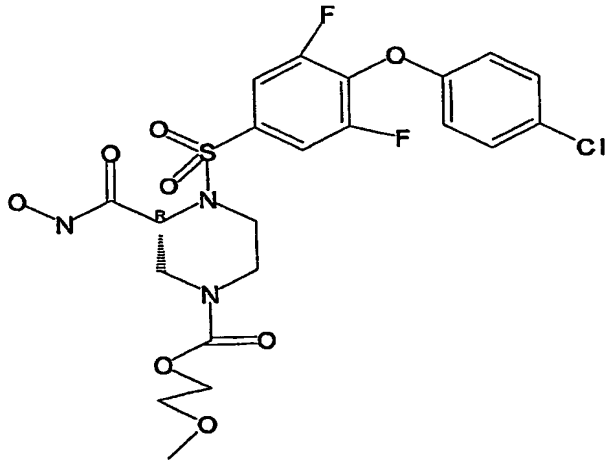
(2R)-1-{[3,5-difluoro-4-(4-fluorophenoxy)phenyl]sulfonyl}-N-hydroxy-4-methyl-2-piperazinecarboxamide,



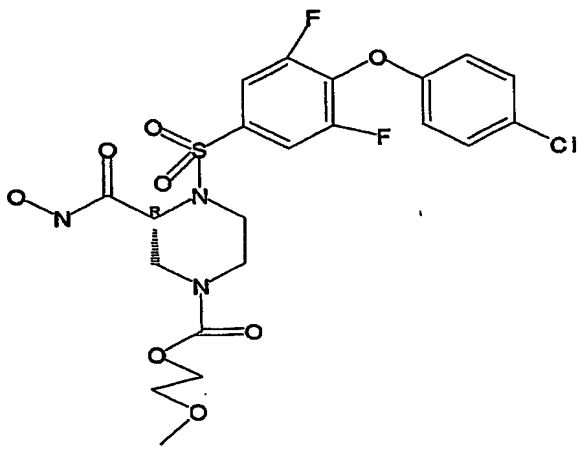
2-methoxyethyl (3R)-4-{[3-fluoro-4-(4-fluorophenoxy)phenyl]sulfonyl}-3-[(hydroxyamino)carbonyl]-1-piperazinecarboxylate,



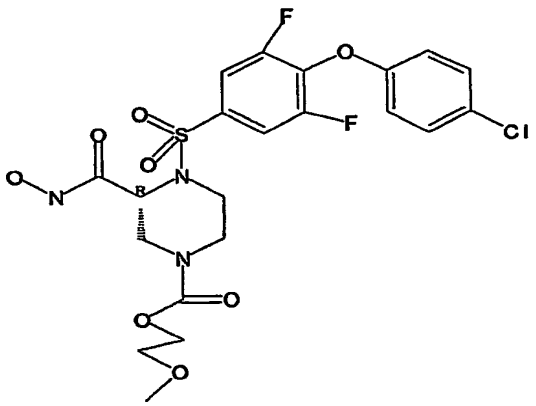
2-methoxyethyl (3R)-4-{[4-(4-chlorophenoxy)-3-fluorophenyl]sulfonyl}-3-[(hydroxyamino)carbonyl]-1-piperazinecarboxylate,



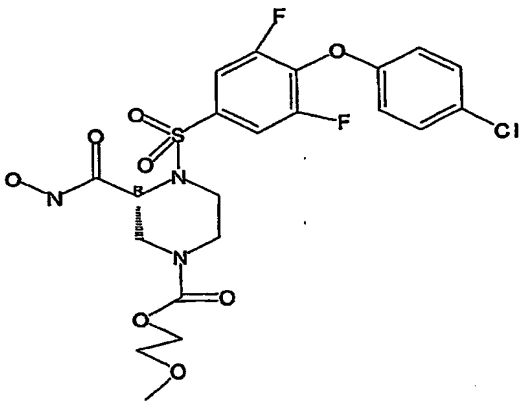
2-methoxyethyl (3R)-4-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-3-[(hydroxyamino)carbonyl]-1-piperazinecarboxylate,



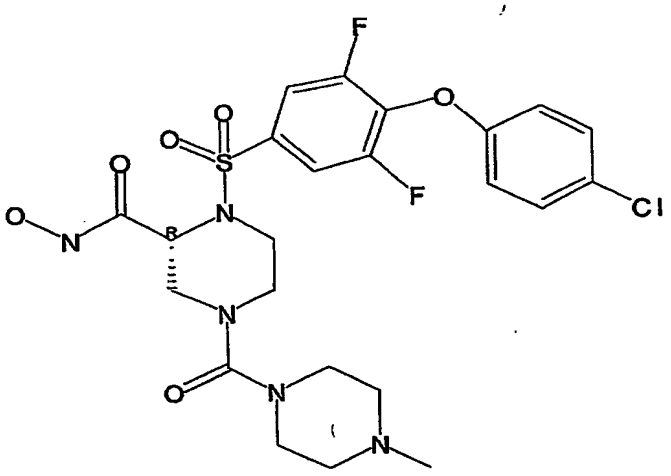
2-methoxyethyl (3R)-4-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-3-[(hydroxyamino)carbonyl]-1-piperazinecarboxylate,



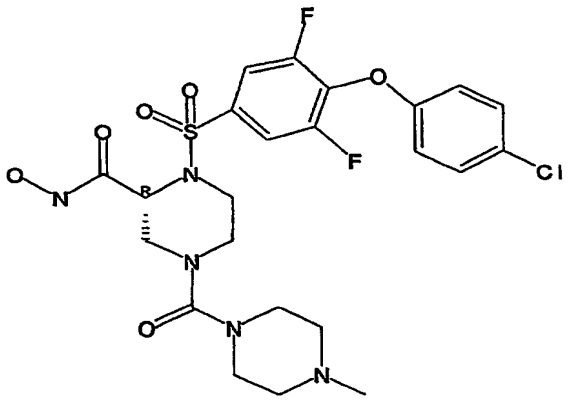
2-methoxyethyl (3R)-4-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-3-[(hydroxyamino)carbonyl]-1-piperazinecarboxylate,



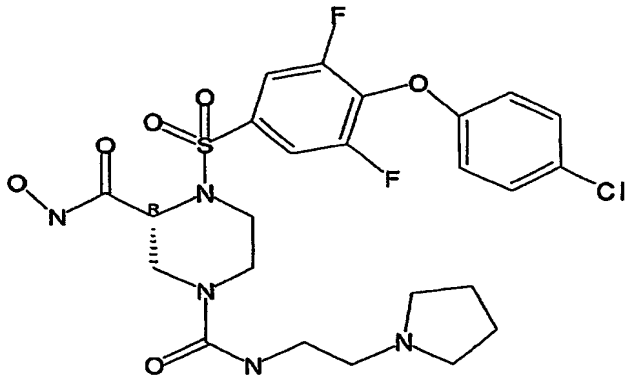
2-methoxyethyl (3R)-4-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-3-[(hydroxyamino)carbonyl]-1-piperazinecarboxylate,



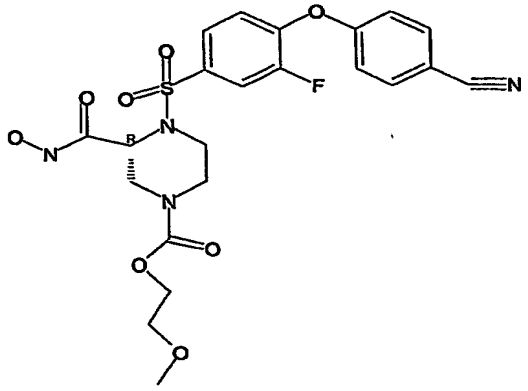
(2R)-1-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-N-hydroxy-4-[(4-methyl-1-piperazinyl)carbonyl]-2-piperazinecarboxamide,



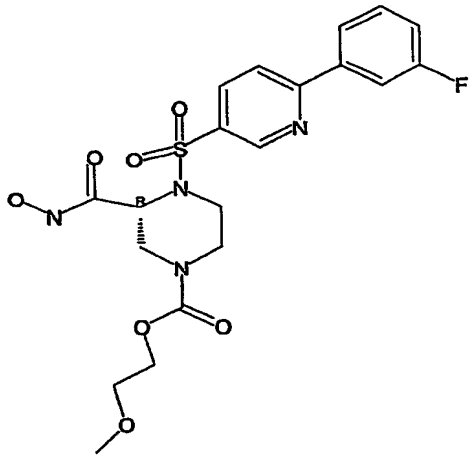
(2R)-1-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-N-hydroxy-4-[(4-methyl-1-piperazinyl)carbonyl]-2-piperazinecarboxamide,



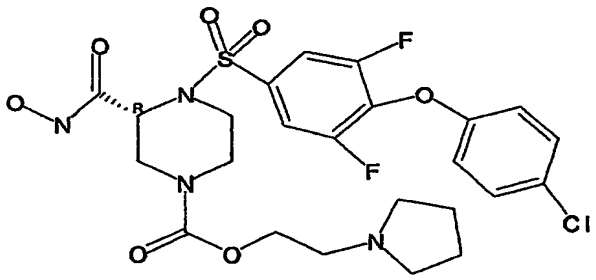
(3R)-4-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-N~3~-hydroxy-N~1~-[2-(1-pyrrolidinyl)ethyl]-1,3-piperazinedicarboxamide,



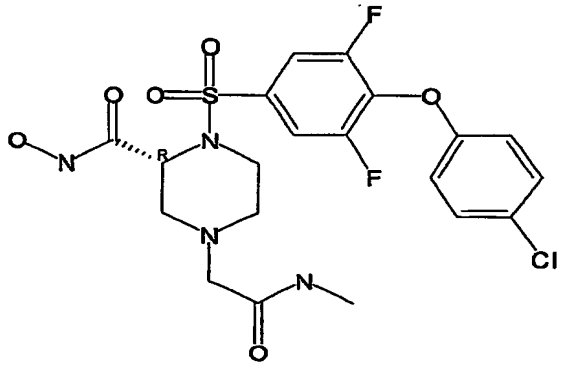
2-methoxyethyl (3R)-4-{[4-(4-cyanophenoxy)-3-fluorophenyl]sulfonyl}-3-[(hydroxyamino)carbonyl]-1-piperazinecarboxylate,



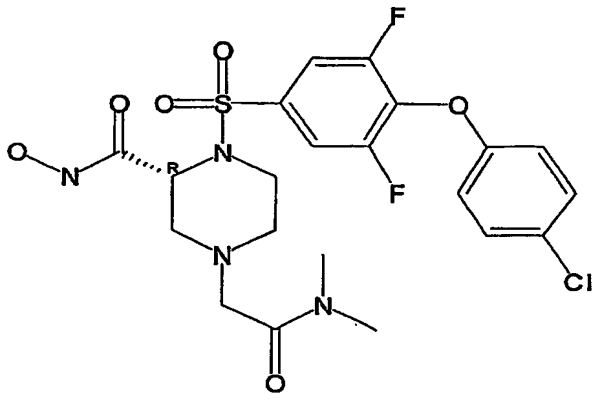
2-methoxyethyl (3R)-4-{[6-(3-fluorophenyl)-3-pyridinyl]sulfonyl}-3-[(hydroxyamino)carbonyl]-1-piperazinecarboxylate,



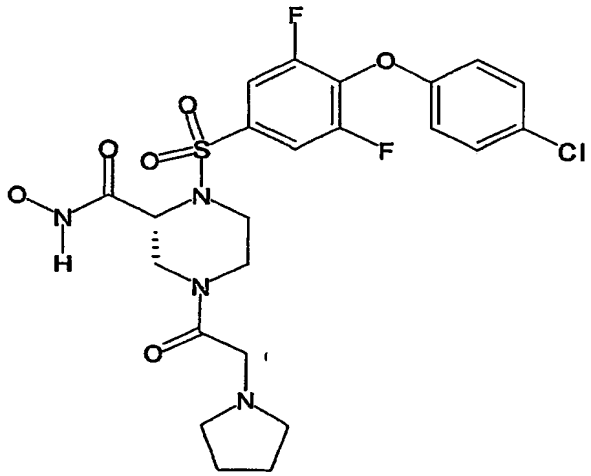
2-(1-pyrrolidinyl)ethyl (3R)-4-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-3-[(hydroxyamino)carbonyl]-1-piperazinecarboxylate,



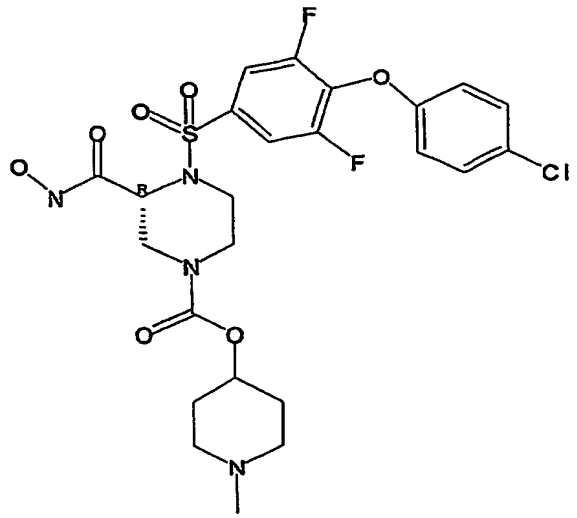
(2R)-1-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-N-hydroxy-4-[2-(methylamino)-2-oxoethyl]-2-piperazinecarboxamide,



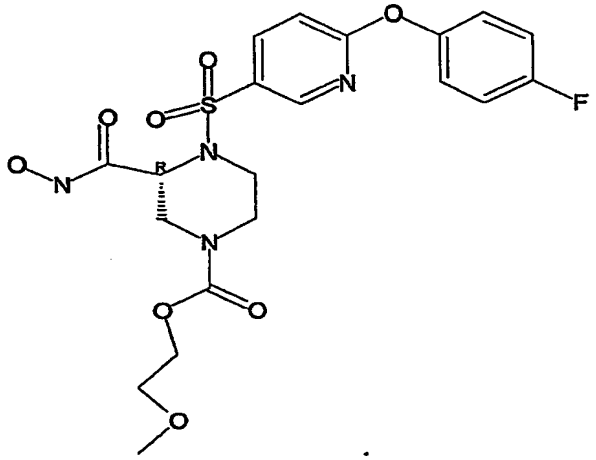
(2R)-1-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-4-[2-(dimethylamino)-2-oxoethyl]-N-hydroxy-2-piperazinecarboxamide,



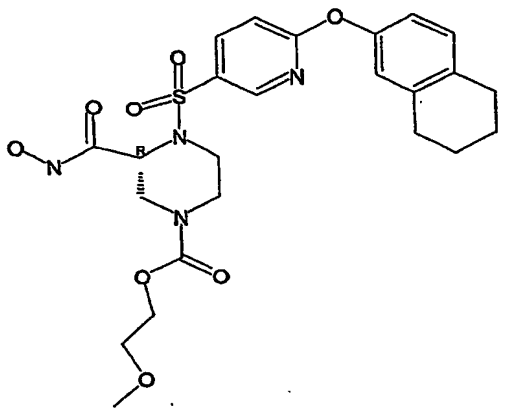
(2R)-1-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-N-hydroxy-4-(1-pyrrolidinylacetyl)-2-piperazinecarboxamide,



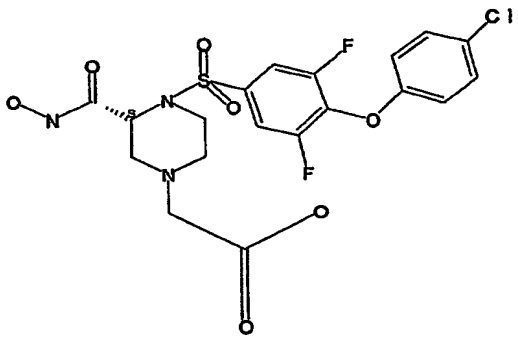
1-methyl-4-piperidinyl (3R)-4-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-3-[(hydroxyamino)carbonyl]-1-piperazinecarboxylate,



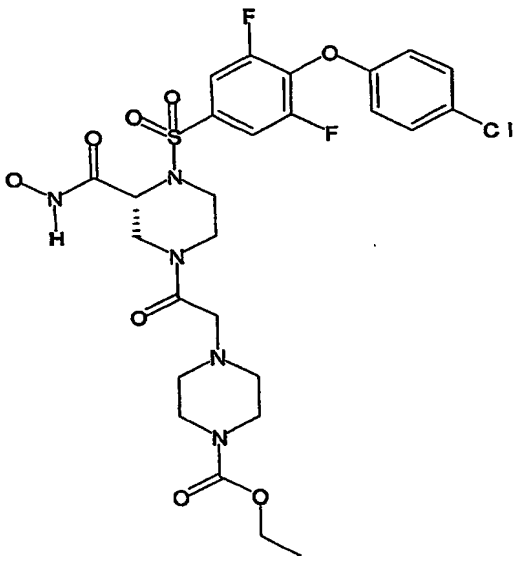
2-methoxyethyl (3R)-4-{[6-(4-fluorophenoxy)-3-pyridinyl]sulfonyl}-3-[(hydroxyamino)carbonyl]-1-piperazinecarboxylate,



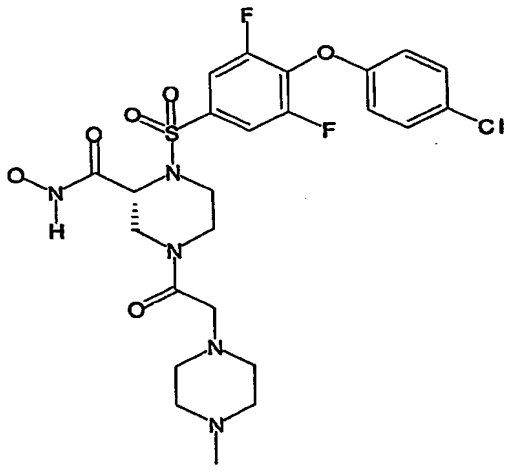
2-methoxyethyl (3R)-3-[(hydroxyamino)carbonyl]-4-{[6-(5,6,7,8-tetrahydro-2-naphthalenyloxy)-3-pyridinyl]sulfonyl}-1-piperazinecarboxylate,



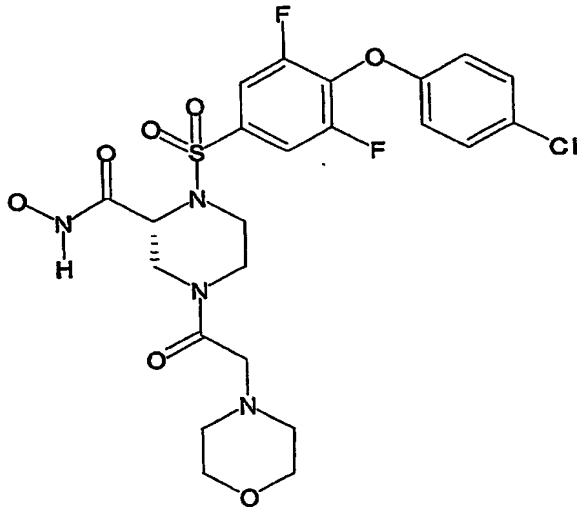
{(3S)-4-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-3-[(hydroxyamino)carbonyl]-1-piperazinyl}acetic acid,



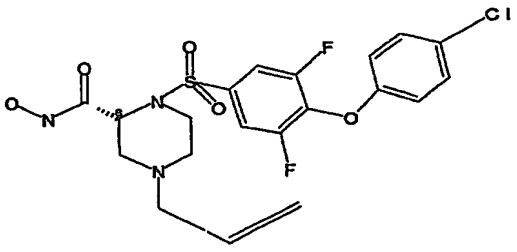
ethyl 4-(2-{(3R)-4-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-3-[(hydroxyamino)carbonyl]-1-piperazinyl}-2-oxoethyl)-1-piperazinecarboxylate,



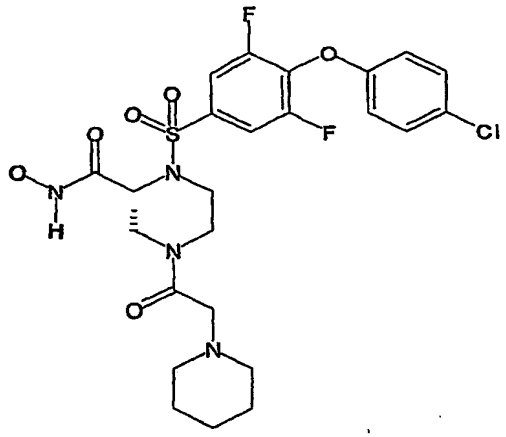
(2R)-1-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-N-hydroxy-4-[(4-methyl-1-piperazinyl)acetyl]-2-piperazinecarboxamide,



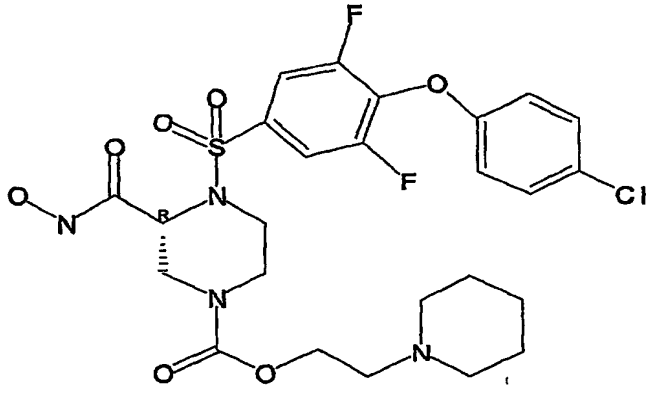
(2R)-1-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-N-hydroxy-4-(4-morpholinylacetyl)-2-piperazinecarboxamide,



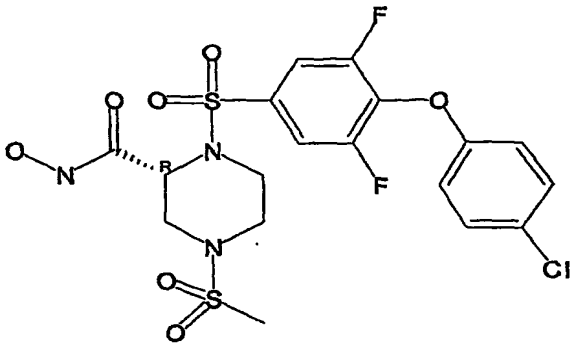
(2S)-4-allyl-1-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-N-hydroxy-2-piperazinecarboxamide,



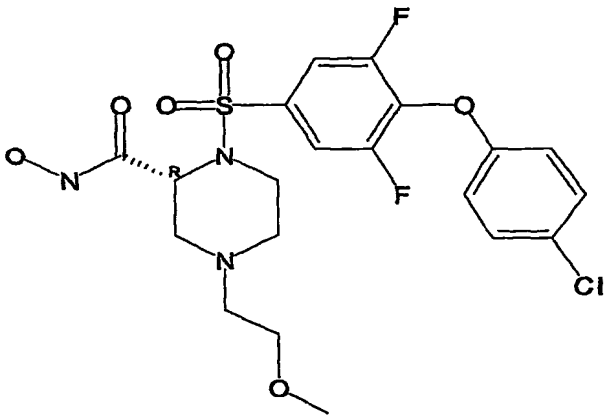
(2R)-1-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-N-hydroxy-4-(1-piperidinylacetyl)-2-piperazinecarboxamide,



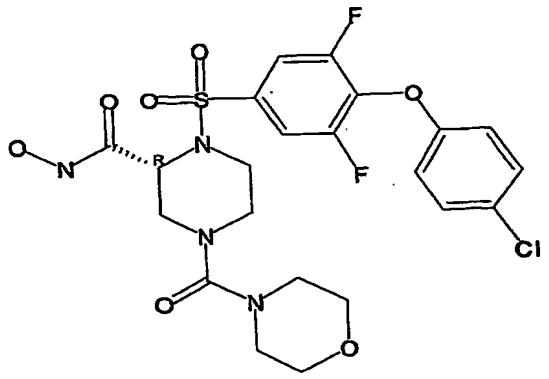
2-(1-piperidinyl)ethyl (3R)-4-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-3-[(hydroxyamino)carbonyl]-1-piperazinecarboxylate,



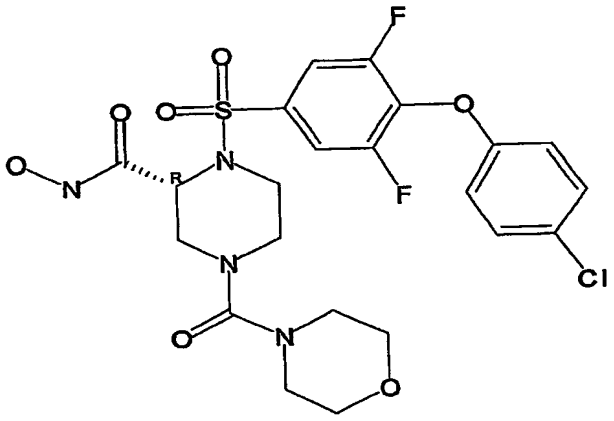
(2R)-1-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-N-hydroxy-4-(methylsulfonyl)-2-piperazinecarboxamide,



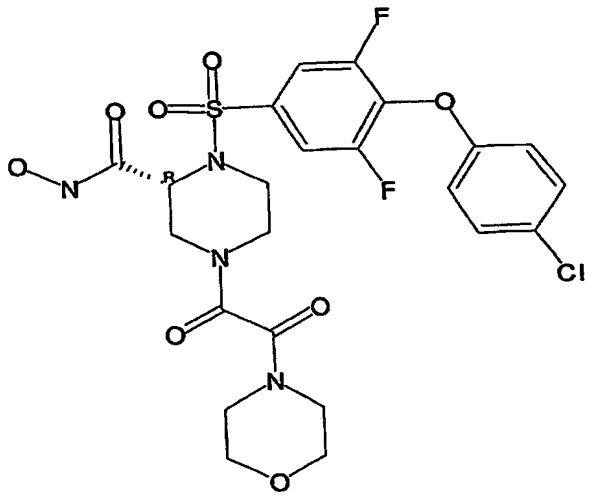
(2R)-1-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-N-hydroxy-4-(2-methoxyethyl)-2-piperazinecarboxamide,



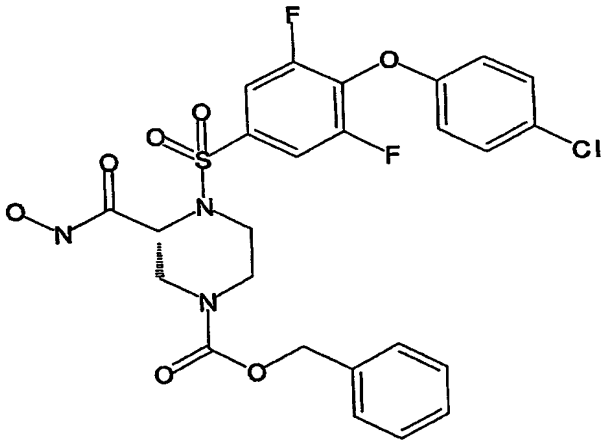
(2R)-1-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-N-hydroxy-4-(4-morpholinylcarbonyl)-2-piperazinecarboxamide,



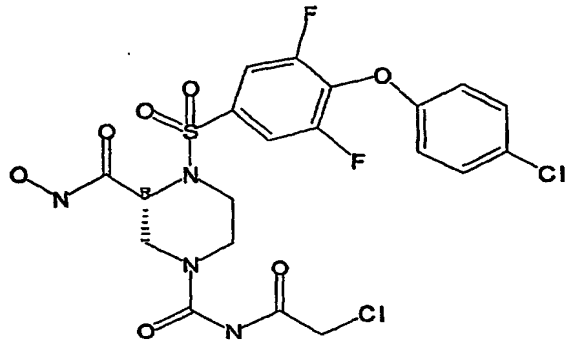
(2R)-1-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-N-hydroxy-4-(4-morpholinylcarbonyl)-2-piperazinecarboxamide,



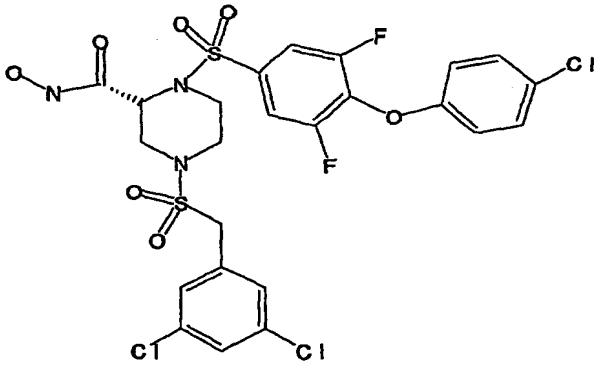
(2R)-1-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-N-hydroxy-4-[4-morpholinyl(oxo)acetyl]-2-piperazinecarboxamide,



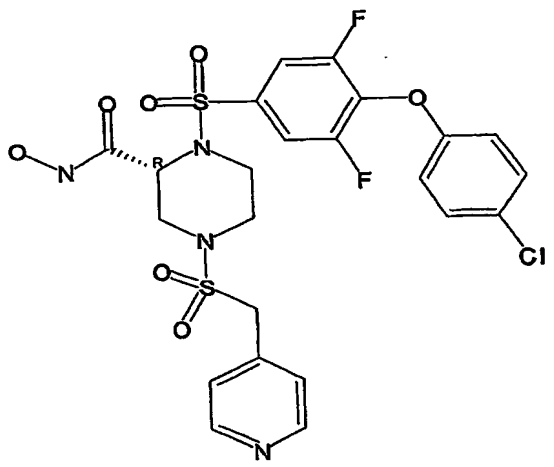
benzyl (3R)-4-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-3-[(hydroxyamino)carbonyl]-1-piperazinecarboxylate,



(3R)-N~1~-(chloroacetyl)-4-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-N~3~-hydroxy-1,3-piperazinedicarboxamide,



(2S)-1-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-4-[(3,5-dichlorobenzyl)sulfonyl]-N-hydroxy-2-piperazinecarboxamide,



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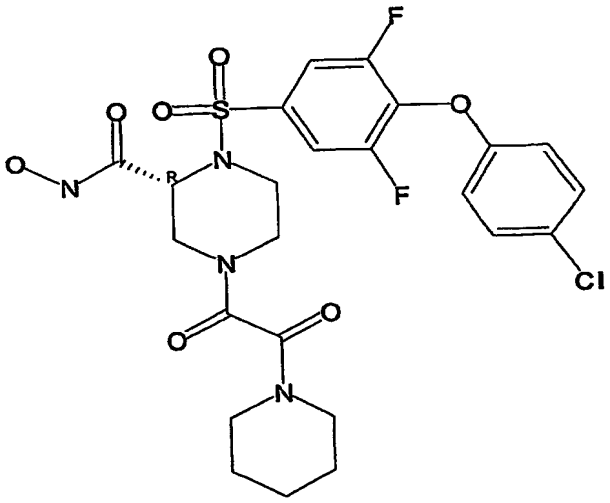
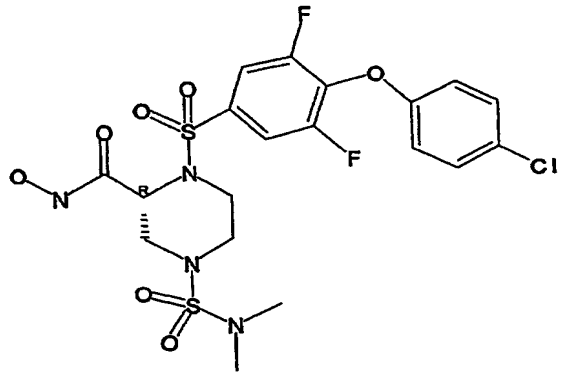
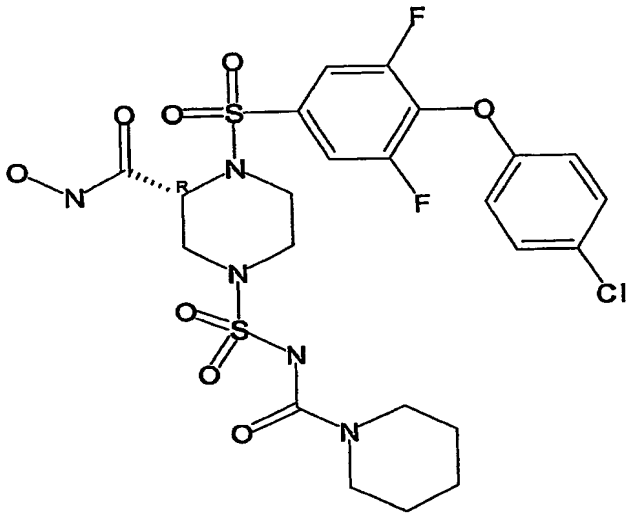


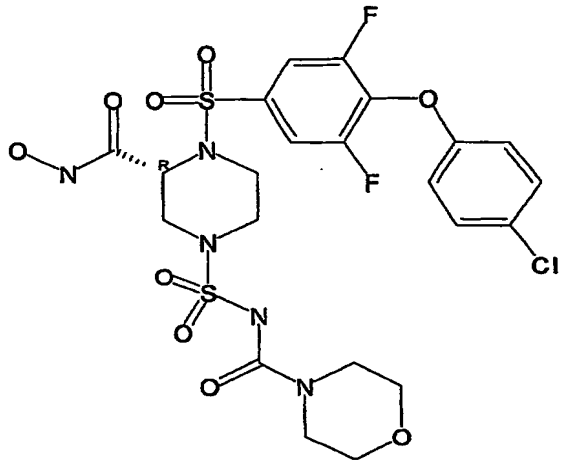
(2R)-1-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-N-hydroxy-4-[oxo(1-piperidinyl)acetyl]-2-piperazinecarboxamide,



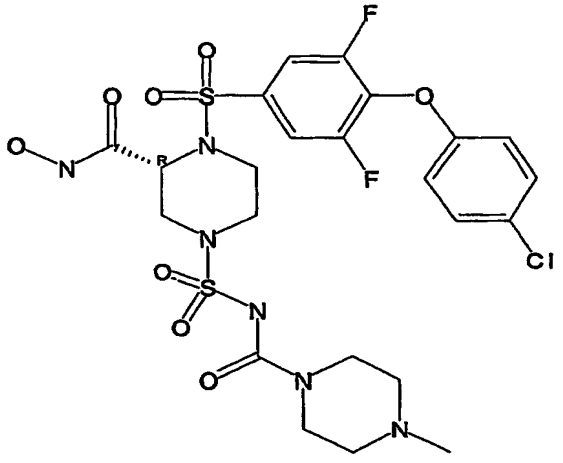
(2R)-1-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-4-[(dimethylamino)sulfonyl]-N-hydroxy-2-piperazinecarboxamide,



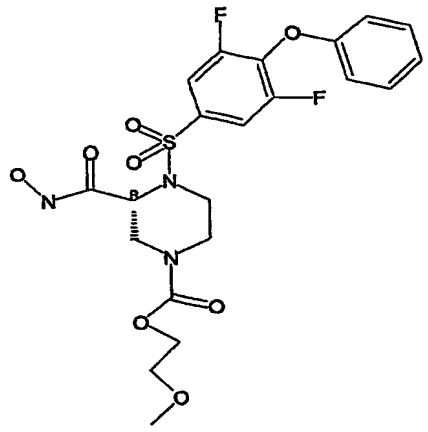
(2R)-1-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-N-hydroxy-4-{[(1-piperidinylcarbonyl)amino]sulfonyl}-2-piperazinecarboxamide,



(2R)-1-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-N-hydroxy-4-{[(4-morpholinylcarbonyl)amino]sulfonyl}-2-piperazinecarboxamide,



(2R)-1-{[4-(4-chlorophenoxy)-3,5-difluorophenyl]sulfonyl}-N-hydroxy-4-{{[(4-methyl-1-piperazinyl)carbonyl]amino}sulfonyl}-2-piperazinecarboxamide, and



2-methoxyethyl (3R)-4-[(3,5-difluoro-4-phenoxyphenyl)sulfonyl]-3-[(hydroxyamino)carbonyl]-1-piperazinecarboxylate.

ABSTRACT OF THE DISCLOSURE

The present invention provides compounds useful for inhibiting the ADAM-10 protein. Such compounds are useful in the *in vitro* study of the role of ADAM-10 (and its inhibition) in biological processes. The present invention also comprises pharmaceutical compositions comprising one or more ADAM-10 inhibitors according to the invention in combination with a pharmaceutically acceptable carrier. Such compositions are useful for the treatment of cancer, arthritis, and diseases related to angiogenesis. Correspondingly, the invention also comprises methods of treating forms of cancer, arthritis, and diseases related to angiogenesis in which ADAM-10 plays a critical role.